

## Toxicological drivers issues in “legal highs” use

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**Abstract:** The regulation and control of psychoactive substances and their precursors is constantly counteracted by the imagination, inventiveness, experimentation and targeted research that consumers/manufacturers use in order to elude the laws, which during the last few years has led to a surge in the marketing and use of these products in the context of a missing or unclear legal framework. We are witnessing an explosion in the use of some products and substances which are either new intoxicants, or have been considered benign until recently (such is the case with numerous species of plants). The legal and medical systems are currently facing conceptual problems: how to define or characterise the product of interest (considering its ubiquitous availability and marketing forms), which of its active principles should be controlled (including by-products created by *spicing* the basic product), which are the applicable criminal, civil or commercial laws, how to control the “rerouting” of pharmaceutical/parapharmaceutical remedies, common drugs, nutritional supplements, exotic aromas, fertilizers or spices – the so-called unconventional intoxicants.

The limitations of scientific knowledge, the novelty of various psychoactive blends, the appearance of new classes of substances, the mix with different plants etc. are major impediments for the increase in the reaction time and consequently for an efficient control by the authorities. In order to provide evidence for intoxication, a certain flexibility is needed for the on-site forensic investigation, analysis of the corpus delicti (toxicology and botanics), and the clinical examination, while toxicological detection may be of support in the context of technical-scientific difficulties. *Driving under influence* thus becomes a challenge for the traffic safety and for the authorities or persons authorised to conduct the inquiry and limit the phenomenon. The present article aims to provide a synthesis of the current scientific knowledge on *legal highs* and an overview of the limitative, but also promising toxicological issues which are needed for the description of the phenomenon.

**Key words:** legal highs, spice, psychoactive substances, hallucinogenic plants

The legal regulation of controlled plants and substances is well established in the whole world, by iterative conventions which list a *pool* of substances, permanently open to updating, anticipating the inherent appearance of new psychoactive substances, even from pharmaceutical research whose results were considered inadequate for human use, or banned from prescription.

This constant counteracting of the quick update of the legal system by the imagination, inventiveness, experimentation and targeted research that consumers/manufacturers use in order to elude the laws has led to a current state of affairs which may be regarded as *alarming* (considering the short period of time which does not allow a description of trends): report of the 24 new substances in 2009, and of other 11 from the family of chemical substances which usually give the new psychoactive drugs: five phenethylamines, two tryptamines, and four synthetic cathinones, plus the use of three new

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pharmaceutical products for hedonistic purposes, comparing to an average of 11 during the last ten years [1]. This is a real challenge for the current monitoring, control and detection systems.

We are witnessing an *explosion* in the marketing of legal or illegal products based on new substances which promise new effects or appear as “legal” substitutes of established intoxicants, but are cheaper or easier to obtain, and possibly with lesser risks for health. The manufacturers of these substances respond impressively fast by introducing new derivatives – still not included on the lists of controlled substances, or new synthesis pathways which do not involve monitored precursors.

The creativity and inventiveness of intoxicant manufacturers render legislation quickly obsolete to new chemical inventions.

The main inconvenience derives from conceptual difficulties: *how to define or characterise the product of interest, which of its active principles should be controlled, which are the applicable criminal, civil or commercial laws* etc. The commercial products are advertised under different names, such as “chemical research substances”, “bath salts” (in sachets of 1-2 g!) “aromatherapy”, “household air fresheners”, “substances intended for botanical research”, “plant food” or “plant fertilizers”, often with the accompanying note “not fit for human consumption”, in order to elude possible control mechanisms for food and/or pharmaceutical safety (although in many cases there are also notes indicating “for recreational use”).

One cannot but notice the obvious contradictions between the pseudo-purpose and the instructions for use, which persuasively list the very effects desired by the user (“*Not all users of herbal drugs may feel the desired effects!!! The effect may vary considerably from one person to another, depending on the body’s resistance to these products. Some persons may experience sensational effects with herbal drugs, while others may have bad trip, or may feel nothing at all.*”, “*The human body’s resistance and reactions may vary considerably from one person to another.*”, “*Excessive use may prove harmful to the body, by causing dizziness, stupor, confusion, and muscle fasciculations.*”, “*To be administered by direct inhalation for recreational purposes, especially to increase sexual pleasure. Inhalation of the product causes relaxation of the body muscles, including anal or vaginal muscles. Furthermore, it increases heart rate and blood flow and creates a heat sensation and intensifies emotions; increases sexual desire, intensifies and prolongs orgasm.*”).

These new products envisaged by hedonistic use may belong to so-called **Unconventional intoxicants**: pharmaceutical/parapharmaceutical benign remedies, common drugs (*Gripex* – contains paracetamol, dextromethorphan, pseudoephedrine, or *Coldrex* – contains paracetamol, promethazine, dextromethorphan), *Tantum Rosa* (topic vaginal antiseptic!!!), nutritional supplements, exotic aromas, fertilizers or spices (re-routed from their indications) – smoked, ingested, infused, *bong*.

The practice of trying common medicinal products which cause psychoactive effects when used in excess, or administered by other route, or blended with other substances or alcohol, has the advantage of being easily available, unmonitored and cheap – antiparkinsonians like *Romparkin*, venlafaxine, fluoxetine, sertraline, citalopram, paroxetine, tramadol, benzydramine (used especially in Poland, Brasil, and Romania as a central nervous stimulant and mild hallucinogen, causes oral and perioral paresthesias, xerostomy, convulsions, euphoria, hallucinations, paranoia, followed by exhaustion and insomnia, in doses of 0.5-3 g orally [2]).

The phenomenon is the result of the proliferation of uncontrolled and unregulated, but growing marketing of substances not included on the list of prohibited substances, in the context of an initially neutral advertising, now facing the spread of a social phenomenon with medical and criminal consequences.

**Spicing** of herbal products is common practice in the marketing of legal highs: a dried and ground herbal product is “spiked” with psychoactive synthesis substances, which are not on the lists of controlled substances.

It becomes obvious in this stage that the classic way to prohibit a generic plant, as done before, is no longer effective – as these are only vectors of added substances which are not adulterants/excipients anymore, but intoxicants as such.

The number of known hallucinogenic plants is over 6,000, plus the synthesis substances!!! It is impossible to control such a vast spontaneous flora, and from a toxicological point of view it is impossible to identify each active principle which determines the psychoactive principles of each plant or blend, or of an administration route, or after preparation (e.g., even *Phalaris arudinacea* – the ordinary grass – may become a source of dimethyltryptamine, an extremely potent hallucinogen, also called *mind-blowing*). The declared content of marketed products refers to ordinary flora – birch, salad, Peru balm, patchouli, laurel, wheatgrass, allspice, hop, etc. Note the ubiquitous availability and the benign character of these plants, and the absence of any known plant from pharmaceutical practice as source of psychoactive substances, which actually supports the theory that effects are due to added excipients.

Here are some plants occasionally declared by the trader as part of the composition, of which only a few may be credited with an intrinsic psychoactive effect [3]:

- *Canavalia Maritima* – L-Betonicine: marijuana-like effect [4,5]
- *Leonotis leonurus* – lion's tail [6]
- *Nymphaea alba* – European White Waterlily [7]
- *Scutellaria nana* [8]
- *Pedicularis densiflora* – Indian warrior
- *Nelumbo nucifera* – Indian lotus
- *Leonurus sibiricus*
- *Althaea officinalis* – marshmallow
- *Rosa canina* – dog rose

These plants may have stimulant, aphrodisiac, psychedelic, sedative, tonic, meditative, entheogen, oneiric, phanerothyme, or metagnomigenic effects.

The law must not wrongfully incriminate the owners of lands where plants grow naturally. These should become “illegal” only when “treated or prepared” – packing is a form of “preparation” (as mentioned in the Ireland and UK legislation), which indicates the intention for marketing/consumption, or, similarly, the Netherlands Supreme Court established that plants are subject to control “dried or processed”. The use is more frequent in *innovator* groups, the ones who are always willing to try new drugs, people with a wide social network, a cosmopolitan lifestyle, fervent dancers, and eager to share their experiences with new substances – the actual *disseminators*. Other category is represented by early adopters of new substances, who are better integrated in society, who respect the *role model*, and are also interested in harm reduction policies. Users are further divided into *early majority – cautious adopters*, *late majority – typically skeptical*, and *laggards* – isolated people, engaged in minimal social activity [9].

Hallucinogens fall into three major classes: ***serotonin 5-HT<sub>2A</sub> receptor agonists*** – serotonergic psychedelics: ergolines (LSD), tryptamine-based compounds like psilocybin, psilocin, and DMT, phenethylamine-based compounds like mescaline and 2C-B; ***serotonin releasers*** – empathogen-entactogens: phenethylamines (methylenedioxymethamphetamine –MDMA); ***cannabinoids***.

From the numerous substances envisaged by regulators, such as C-I (2,5-dimethoxy-4-iodophenethylamine), 2C-T-2 (2,5-dimethoxy-4-ethylthio-phenethylamine), 2C-T-7 (2,5-dimethoxy-4(n)-propylthio-phenethylamine), PMMA (parametoxymethamphetamine or N-methyl-1-(4-methoxyphenyl)-2-aminopropane), TMA-2 (2,4,5-trimethoxyamphetamine), some have been initially considered for therapeutic use by Shulgin (*Phenethylamines I Have Known And Loved: A Chemical story – PiHKAL*, 1991[3]), having a similar composition to phenethylamines, which give a mixture of stimulant and hallucinogenic effects [10].

During the last 40 years, the pharmaceutical industry has developed relatively obscure substances with similar effects, which have not been subject to international control, like delta-9-tetrahydrocannabinol THC [11] – obtained by synthesis, but with different and varied chemical structures (based on a dibenzopyran ring), falling into the large category of synthetic cannabinoids – for medical use, particularly as analgics. Failure to obtain a product with a favourable risk/benefit ratio precluded further development (risks include undesired and intense psychoactive effects,

obtained by the same pharmacological processes as with THC, by stimulating cannabinoid receptors in the SNC), but they were introduced on the black market as potent highs with the great advantage of not being included on the lists of controlled substances.

One of the first such substances was synthesised in the '60s and called HU-210 (HU stands for Hebrew University), from the class of *nabilone* and *dronabinole*, rarely used in clinical practice as antiemetics, but having a psychoactive potency 100 times greater than THC. Subsequently in the '70s, Pfizer developed the cyclohexylphenols, e. g. CP-59540, CP-47497, known as *non-classical* cannabinoids.

In 1990, J. W. Huffman from Clemson University, USA created the classes naphthoylindoles, naphthylmethylindoles, naphthoylpyrroles, naphthylmethylindenes, and phenylacetylindoles (benzoylindoles), known as aminoalkylindoles or JWH compounds, from the name of the researcher. [12] JWH 250 was identified in a larger number of confiscated *legal highs* [13, 14].

Other products revealed fatty acid amides – oleamides – with a structure similar to anandamides (cannabinoid ligands), some of which are also used in plastic materials (antiglide).

Furthermore, the first clinical intoxication cases with new substances derived from cathinone were reported in Europe in 2007 and involved mephedrone, methylone, methedrone, and MDPV. These “synthesis” compounds are derivatives of cathinone (a Schedule I drug under the Convention on Psychotropic Substances of 1971), found in the shrub khat (*Catha edulis*), and structurally related to amphetamine.

Mephedrone (methcathinone – 4-methyl-*N*-methylcathinone) – 4 MMC – marketed under a number of street names, such as *Miaow*, *Miow*, *4-methylmethcathinone*, *Mephedrone*, *Methedrone*, *Mephadrone*, *MM*, *cat*, *Miau*, *Meow*, *Plant feeder*, *Snuff*, *Plant Food*, *Snow*, *Special Gold*, *Magic Powder*, *Flower Power*, *Charge+*, *Blue Magic Star*, *Cristal*, *Star*, *Blast*, *Dust*, *White*, *Feeder* – police captures reveal it as white to yellowish powder crystals, with an unpleasant odour described as a mixture of chloride, vanilla, and urine. The substance is frequent and a few studies have been attempted to clarify the specific toxicological and clinical issues.

*Betahydroxylated* metabolites (*paramethyl ephedrine*), *betahydroxy-N-demethylates* (*paramethylnorephedrine*), which are structurally related to amphetamines and ephedrine, are probable and expected. Metabolism involves *N*-demethylation to primary amines, reduction to ceto-alcohols, and oxidation of toluene derivatives corresponding to alcohols and carboxylic acids. Elimination is predominantly renal, with a minimal concentration in other compartments. Metabolites are responsible for toxicity: *paramethyl ephedrine* is 2.27-3.4 times more toxic than ephedrine. The half time of *cathinone* is 1.5 h, and by metabolisation it forms betahydroxy metabolites with a half time of 5 h; thus, multiple doses do not increase concentration of cathinone, but add to metabolite concentration [15].

Mild sympathomimetic (amphetamine-like) effects have a large interpersonal and intrapersonal (between episodes) variation: omnipotence, aphrodisiac, relaxation, floating, euphoria, visual alterations to visual hallucinations, alteration of perception and disposition vs. agitation, tenseness, anxiety, alteration of reasoning, depersonalisation, panic reaction, paranoia, pseudo-psychosis (bad trip), with a risk of suicide and accidents.

Other possible reactions are epistaxis, nasal pain or burn sensation, xerostomy, chemosis, rash, diaphoresis, nausea, vomiting, diarrhoea, abdominal pain, tremor, trismus, bruxism, dizziness, headaches, weakness, muscle pain, chills, mydriasis, tachycardia, tachypnoea, increase in blood pressure (following peripheral vasoconstriction – possibly related to 4-methyl ephedrine metabolite, which has a higher cardiovascular toxicity than ephedrine), rarely the loss of consciousness, psychomotor agitation, with or without motor alterations. Fast tolerance buildup to dose increase, dependence and severe adverse reactions.

New substances revealed in 2010 in Europe include methylenedioxyprovalerone (MDPV), naphyrone, and other naphthylprovalerone analogues, and 2-DPMP (desoxypipradrol).

A significant decrease has been noticed in cases which involve MDMA (ecstasy), correlated to an increase in the use of new substances (58 cases with mephedrone and MDVP in the UK) [16]; this evidence supports the progressive trend of replacing controlled products with legal products.

In the absence of clinical and toxicological profiles, it is difficult to establish the real life-threatening risk of these new substances; however, when looking at the quoted effects (especially the cardiovascular ones), their contribution to the medical cause of death is presumable.

The determination of substances of the above mentioned classes was made possible for *legal high* products, in which they can be added either into the herbal blend or benign powder/crystals. Actually, the psychoactive effect is due in part or, in some cases, even entirely to the excipients added by “spiking” and not to the declared content of herbs.

European laboratories with state-of-the-art equipment (such as tandem mass spectrometry – MS/MS, and spectroscopy with Nuclear Magnetic Resonance – NMR), sometimes accompanied by a happy turn of events (JWH-018 was revealed because of a reference standard found in the archive of the pharmaceutical company which created it, and thus researchers succeeded to compare spectres for the incriminating evidence), managed to identify these substances only occasionally and for research purposes, not for current testing; however, the whole spectrum of additives from the marketed products is not known, and testing is still far from becoming routine practice [17].

Tolerance to synthetic cannabinoids may develop very fast, and in the absence of any large clinical studies, there is a lack of objective data to evaluate these effects. Considering the high potency and the unpredictable level of these substances in the marketed products, plus the possible addition of other psychoactive substances and the development of tolerance, we can associate them with psychoactive episodes or hallucinogenic manifestations, however we cannot be sure of the relationship between dose and the intensity of effects in the absence of targeted studies and relevant toxicological assays.

Information comes mostly from *trendsetters’* postings on sites/forums/blogs, because sporadic medical reports cannot help building specific profiles, in the absence of structured research. One of the major drawbacks to understanding the phenomenon is the lack of information on the clinical manifestations and their intensity, which may be attributed either to the class, or more often to the specific substance, due to the fact that the marketed products are spiced inconsistently with a blend of substances which may vary in quality or amount.

There are currently no extended prospective or questionnaire studies to help building clinical specific profiles, but only sporadic case reports. The *legal high* intoxication cannot be specifically attributed to a certain substance, as long as:

- the actual composition of the product is different from the package specifications, and it is not known: the stated herbal blend appears to defy medical common sense, while plant scientific names are translated for the public: spontaneous flora and common nutriments, with no psychoactive value. No botanical studies confirm or contradict conformity with the stated composition. Similarly to the black market practice, the product may be also substituted with anything else, and the official benign herbal product can actually be blended or replaced with psychoactive products.
- The percentage composition is not known for each plant, which makes the selective analysis of their effects or intensity impossible.
- The (officially stated) inconsistency of composition for the same product.
- The marketing of products from different manufacturing sources under the same name.
- The active principle which provides the psychoactive effect is not known
- The pooled effect of a herbal blend is not known
- The administration route is inconsistent – snuff or ingestion of native content, or pyrolysis/injection after *preparation*

*Importantly, there are no officially published safety data and almost nothing is known about their effects in humans.* – EMCDDA, 2009 [18].

The clinical profile of intoxications covers a wide spectrum, related to the biochemical mechanism of action (inferred from the chemical structural analogies with known drugs or studied, in some cases):

- partial agonism of serotonin 5-HT receptors (which stimulate hypothalamic neurons involved in controlling the secretion of ACTH and cortisol, but also of the growth hormone and prolactin – similar to mescaline and DOM); potent hallucinogenic stimulants (psychedelic effects, empathy, affective sensitiveness– pleasant introspection state, easy communication, compassion); in high doses – hypomotility, hypophagia, anxiety, hyperthermia, priapism, hallucinations. Mescaline-like hallucinogenic effects (*the whole mescaline package, less the colour imagery*) and MDMA-like empathic effects [19] are accompanied by nausea, vomiting, abdominal pain, diarrhoea, muscle cramps, disorientation, anxiety, tremor, hypothermia, bradycardia, hypertension [20], suffocation, dizziness, floating, fear, depression, aggression, persecution, psychic discomfort – anxiety,
- partial agonism of alpha-1-adrenergic receptors – agitation, aggression, violent behaviour.
- potent serotonin releaser from the neurons and serotonin/noradrenaline reuptake inhibition, which may lead to repeated use, neuronal depletion, with occurrence of serotonergic syndrome-related signs – agitation, hyperreflexion, hindlimb abduction, head-twitching, rigidity, gait disorders, tremor, goose bumps, seizures, coma, death – risks increase with ketamine co-administration.
- MAO-A inhibition elevates central noradrenaline: explains prolonged cardiovascular effects – hypertension, persistent tachycardia – typical sympathomimetic status, including excessive salivation, excessive tearing, goose bumps, nausea, nistagmus, hyperthermia, thirst, chills, increased intraocular pressure, confusion, memory disorders, coma, heart attack [21], seizures; the major risk is brought by dose-dependant hyperthermia. Other possible effects are hyperreflexion, nistagmus, muscle contractions, bruxism, nausea, headaches, ulcer pain.

The homolythic/heterolytic risk of clinical manifestations is obvious from the description above, as are the inherent risks of pharmacological effects, some of which are fortunately rare, but at the same time life-threatening. Cardiovascular effects, seizures, hyperthermia and dehydration require life support measures in a hospital environment. Marked psychic effects, possibly transient psychotic episodes, are the disabling component, incompatible with an adequate responsibility and with some professions, including driving.

A real challenge for forensic examiners and legal professionals to obtain evidence of intoxication arises from the increase in cases reported by traffic police of intoxicated drivers with no alcohol in the expired air, with more or less specific objective clinical elements, and sometimes accompanied by the finding of legal highs paraphernalia or packaging in the glove compartment.

Spicing *legal highs* with new substances, which are yet not included on the list of controlled substances, represents **a major challenge to toxicology**. The difficulty of detection (currently the main hindrance of a consistent and prompt reaction in order to control the phenomenon) occurs at every stage of the good toxicological practice (limitations of the medical science, technical/financial limits, and equipment limitations):

- New substances, with unknown chemical formula and reactivity
- Lack of information on the actual composition of tested products
- The inconsistency of composition and dosage for the same product
- The use of a vector substrate of a plant which is an independent chemical universe in itself, and in some cases may also contain psychoactive substances, other than the synthesis-added ones
- Blends of numerous plants which theoretically may have psychoactive effects, but we do not know to which chemical element they are attributable
- Bioavailability, pharmacodynamics, and pharmacokinetics of these new substances are unknown, as well as the intermediate and final products of their metabolism
- Pyrolysis/volatilisation alter the basic substance

- Doses are infinitesimal – which requires highly sensitive determinations – expensive equipment (tandem mass spectrometer), high cost per assay (over 1,000 EUR), continuous workflow (and demand is scarce at the moment)
- Difficulty to extract an unknown mixture of chemical elements from a complex matrix
- The intentional addition of adulterants for masking the presence of other substances
- Substances not present in the UV-spectral database of laboratory equipment
- Lack of specific standards – very high cost per standard (thousands of Euro for a single substance)
- Ineffective screening – no cross reactions with existent immunoassay antibodies

Very few laboratories in the whole world developed methods for detecting synthetic cannabinoids from the incriminating evidence, and fewer from blood, but not from urine, which limits even more the detection possibilities outside the acute intoxication episode.

Cases recently reported include both obvious cases of intoxication in drivers stopped in traffic, or aggression situations – revealing a general profile characterised by delirium-hallucinations or psychomotor agitation, accompanied by suggestive incriminating evidence (packages, butts of manufactured cigarettes, paraphernalia, even herbal or crystal residues), sometimes corroborated with testimonies and declarations. In daily practice, when a toxicological assay would be the only means to prove intoxication, such cases are deficient of the most valuable evidence.

Current problems:

- Failure to prove the use of such substances by performing a toxicological assay on biological samples
- The need for a legal regulation of the evidence of use: a greater weight of the inquiry data, on-site research and medical clinical – forensic examination, which notes the medical issues of acute intoxication
- The immediate inclusion of the newly detected substances in the lists of controlled substances
- Radical change of legislation for the marketing of such products, specifically requiring the submission of certificates of conformity referring to the actual composition by presenting competitive laboratory assays
- The need for a botanical examination of the corpus delicti.

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