New psychoactive substances: are we challenged by new paradigms or just a face lift of old drugs of abuse?
The worldwide status quo on drug abuse has changed dramatically in recent years, with the appearance of a wide range of new psychoactive substances, collectively known as “legal highs”, sold via the internet or at “smart shops” or “head shops”
During 2013, 81 new psychoactive substances were notified by the Member States for the first time through the EU Early Warning System. The unprecedented speed of appearance and distribution of the NPS worldwide makes it difficult or even impossible to assess its hazards and social risks and therefore a good understanding of the potential harm of these substances is still to be evaluated.
Fallacies about NPS

1. “NPS are different from classical drugs of abuse, and its use involves lower health risks”

2. “NPS sold in smartshops are more pure than street drugs”
Are we challenged by new paradigms from the pharmacological and toxicological point of view?

NO

The receptors/transporters are the same

Only variations in potency and/or mixed effects are to be expected
Dependence pathways are the same
Development of psychotic and schizophrenic states are a strong risk caused by drug use during the development of the pre-frontal cortex.

Fallacies about NPS

“NPS are different from classical drugs of abuse, and its use involves lower health risks”

In reality:

If chemical structures of NPS are similar to those of illegal drugs, or whether they have the same pharmacodynamics, the negative effects will be at least similar, if not even worse
Chemical structure of cathinone/amphetamine derivatives

- Cathinone
- Methamphetamine
- Amphetamine
- 4-Methylthioamphetamine
- Phenylethylamine
- Methylenedioxymethamphetamine (MDMA; Ecstasy)
- Catecholamines
- Serotonin

Catha edulis

Cathedulis
Mechanism of action of amphetamine derivatives – release of neurotransmitters from nerve endings
Serotonin

SERT

Basal neurologic activity
(normal)
Fase III

- **ECSTASY**
- **Serotonin**

Pharmacological effect of short duration

Hyper-stimulation of receptors
Cathinone/amphetamine-like “legal highs”

- 2-Methylmethcathinone (2-MMC)
- 3-Methylmethcathinone (3-MMC)
- 4-Methylmethcathinone (4-MMC or Mephedrone)
- 4-Methoxymethcathinone (Methedrone)
- Flephedrone
- Cathinone
- Amphetamine
- Buphedrone
- 3,4-Methylenedioxyn-N-methylcathinone (Methylone)
- Ecstasy
- Butylone
- 5,6-Methylenedioxy-2-aminoindane (MDAI)
- Methylenedioxypyrovalerone (MDPV)
- Naphyrone
Mephedrone and Methylone Increase Extracellular Serotonin and Dopamine, similarly to MDMA

Monoamine oxidase-mediated metabolism of monoamine neurotransmitters causes severe oxidative damage to brain mitochondria.

Monoamine oxidase (MAO) catalyzes the metabolism of monoamine neurotransmitters like serotonin (5-HT) to form 5-hydroxyindoleacetaldehyde (5-HIAL) and 5-hydroxyindoleacetic acid (5-HIAA). The reaction involves the generation of hydrogen peroxide ($\text{H}_2\text{O}_2$) which leads to the formation of hydroxyl radicals ($\text{HO}^-$) that cause oxidative damage to DNA and mitochondria.
Monoamine oxidase-mediated metabolism of monoamine neurotransmitters causes severe oxidative damage to brain mitochondria.
Oxidation of brain mitochondrial proteins and prevention by a MAO-B inhibitor

Ecstasy – Increase of free intracellular calcium in hippocampal neurons
In neurons, mitochondria are highly dynamic organelles

Mitochondrial movement in a hippocampal neuron, at 6 DIV, under control conditions. Live-imaging was performed in a hippocampal neuron transfected with MitDsRed.
Ecstasy dramatically impairs mitochondrial trafficking in hippocampal neurons

(A-B) Axonal transport of mitochondria in a hippocampal neuron, at 6DIV, under control conditions (A) or after exposure to MDMA for 90 min (B). Live-imaging of axonal mitochondria was performed in a hippocampal neuron transfected with MitDsRed.
MDMA is metabolized in the liver, resulting in the formation and release of toxic metabolites to the circulation.
Production of hydrogen peroxide in Mouse brain synaptosomes

The metabolites of ecstasy are much more neurotoxic

Exposure to MDMA may elicit long-term changes in the neurochemistry and behaviour resulting from selective neurotoxicity of serotonergic axon terminals.
The same type of metabolism is expected for NPS with the 3,4-methylenedioxyl group.
Amphetamine derivatives - wanted effects

Euforia

Entactogenic - peacefulness and thoughtfulness

Empathogenic – Emotional link to the surrounding people

Increased perception of all senses: vision, hearing, smell, taste, touch
Possible neurological and behavioral consequences for consumers of amphetamine derivatives

- Memory deficits and loss of cognitive faculties
- Panic Attacks
- Emergence of psychotic states, often of paranoid nature, up to schizophrenic states
- Convulsions
- Sympathomimetic/dopaminergic/Serotoninergic syndrome
- Hallucinations
- States of anxiety and depression, sometimes accompanied by violent and impulsive behavior, sleep problems and anorexia
- Accelerated brain aging?
Teratogenicity and embryotoxicity

Rhabdomyolysis

Disseminated Intravascular Coagulation

Neurotoxicity

Teratogenicity and embryotoxicity

Hyponatremia

Toxicity to the cardiovascular system

Hepatotoxicity

Nephrotoxicity

Hyperthermia
chemical structure of serotonin and of other hallucinogens

Peyote cactus

Mescaline

Serotonin

psilocybin

MDMA

Lysergic acid diethylamide (LSD)

Stimulation of 5-HT2A receptors, especially in pyramidal neurons of the neocortex

Synthesized by Hofmann, in 1938

Magic mushrooms
Psilocybe cubensis
Psilocybe mexicana
DOI (2,5-Dimethoxy-4-iodoamphetamine, an hallucinogenic mescaline derivative and agonist of 5-HT$_{2A}$ receptors induces apoptosis in cortical neurons – prevented by 5-HT$_{2A}$ antibodies
Are we challenged by new paradigms from the Analytical Chemistry point of view?

YES

Structures and solubility of NPS are different from classical drugs

The profile of NPS metabolites will sustain several differences

Mixtures of different NPS are frequent
Pharmacokinetic features

Generally, the presence of the $\beta$-keto group increases the polarity of the synthetic cathinones, resulting in a decrease of their ability to cross the blood-brain barrier (BBB).

Higher or repeated doses are used…
Pharmacokinetic features

The polarity issue occurs mainly with the N-alkylated derivatives, but not so much with the pyrrolidine family of cathinones, since the presence of the pyrrolidine ring greatly reduces the polarity of these compounds.
Mitragynine and 7-Hydroxymitragynine are agonists of opioid receptors delta and mu. At low doses, they act as adrenergic agonists. At high doses, they function as opioid agonists. Both are 30 and 17 x more potent than mitragyne and morphine, respectively. Mitragyna speciosa (Kratom) is a plant extract with opioid activity. Mixtures of these compounds are used in various forms, including extracts.
Mixtures

Plant extracts with opioid activity

KRATOM + O-Desmethyltramadol

Considered the cause of several deaths in Sweden
Mixtures of different NPS are frequent.
Mixtures have been shown to be more toxic

PRIMARY CULTURES OF RAT HEPATOCYTES

Toxicity of Bloom, Blow and MDMA

4-MEC - 4-Methylethcathinone
MDPV - Methyleneoxytryptophorone
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Salvia divinorum

Salvinorin A:

Agonist of kappa opioid receptors

Kappa opioid agonists cause hallucinogenic effects often unpleasant (or even dysphoric)
Effects appear within one minute after administration of the drug:
Dysphoria, hallucinations, dissociation, uncontrolled laughter, depersonalization.
CATHINONE/AMPHETAMINE DERIVATIVES

OTHER TOXIC EFFECTS IN ANIMAL STUDIES

Cardiovascular toxicity
Mephedrone increases the heart rate and blood pressure in rats, and cardiac contractility in guinea pigs

Thermoregulation
Cathinone, ephedrone and methylone induce hyperthermia in rats
MDPV evokes a dose-dependent hyperthermia in mice, but only at a warm ambient temperature
Mephedrone induces hypothermia in single doses, and hyperthermia in a binging session

Addictive and reinforcing effects
Mephedrone and MDPV elicit self-administration patterns in rats
Methyline shows a dose-dependent reinforcer efficacy in rats
CATHINONE/AMPHETAMINE DERIVATIVES

SUBJECTIVE EFFECTS AND ADVERSE TOXIC REACTIONS IN HUMANS

**Synthetic cathinones**

Subjective effects: euphoria, increased empathy, decreased sense of hostility, and increased libido

Unwanted effects: sweating, nausea, vomiting, headaches, dizziness and confusion

Toxic effects

*Cardiovascular* – hypertension and tachycardia, hyperthermia, peripheral vasoconstriction, palpitations, chest pain, tremor and seizure

*Neurological* – agitation, hallucinations, aggressiveness, anxiety, restlessness, depression with suicidal ideations, psychosis, anhedonia and dependence

*Other* – mydriasis, hyponatraemia, acute liver failure, acute kidney injury and rhabdomyolisis