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DE
MÉDICOS FORENSES

Spanish Journal of Legal Medicine

Revista Española de Medicina Legal

www.elsevier.es/mlegal



REVIEW

New psychoactive substances: Popular and dangerous[☆]

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Received 30 August 2017; accepted 29 November 2017

KEYWORDS

New psychoactive
substances;
Effects;

Abstract New psychoactive substances (NPS) have become increasingly popular, despite the potential harm associated with their use. Due to its unknown profile, it is of vital importance that any toxicological data collected is shared, in order to understand the effects associated with the use of these substances, and this data are shared with the scientific community in

DOI of original article: <https://doi.org/10.1016/j.reml.2017.11.004>

Abbreviations: 25B-NBOMe, 2-(4-bromo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl) ethanamine; 25C-NBOMe, 2-(4-chloro-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl) ethanamine; 25I-NBOMe, 2-(4-iodo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl) ethanamine; 2C-B, 4-bromo-2,5-dimethoxyphenethylamine; 2C-I, 4-iodo-2,5-dimethoxyphenethylamine; 2C-P, rel-2-[(1R,3S)-3-hydroxycyclohexyl]-5-(2-methylnonan-2-yl) phenol; 2C-T, 72,5-dimethoxy-4-n-propylthiophenethylamine; 3MMC, 3-methyl-N-methylcathinone; 4,4'-DMAR, 4,4'-Dimethylaminorex; 4-FA, para-fluoroamphetamine; 4-MEC, 4-methyl-N-ethylcathinone; 4-MTA, 4-Methylthioamphetamine; 5-6APB, 6-(2-aminopropyl) benzofuran; 5F-ADBINA, N-1-naphthalenyl-1-pentyl-1H-indole-3-carboxamide; 5F-AMB, (S)-methyl-2-(1-(5-fluoropentyl)-1H-indazole-3-carboxamido)-3-methylbutanoate; 5F-PB-22, Quinolin-8-yl 1-pentyl-1H-indole-3-carboxylate; 5-HT1, serotonin receptor; 5-HT2, serotonin receptor; 5-IAI, 5-iodo-2,3-dihydro-1H-inden-2-amine; AB-CHMINACA, N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide; AB-FUBINACA, N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide; AH-7921, 3,4-dichloro-N-[[1-dimethylamino]cyclohexyl]methyl]benzamide α -PVP α -Pyrrolidinopentiophenone; AM-2201, (1-(5-fluoropentyl)-3-(1-naphthoyl) indole; AM-694, [1-(5-fluoropentyl)-1H-indol-3-yl] (2-iodophenyl) methanone; BZP, 1-Benzylpiperazine; DEA, Drug Enforcement Administration; LD50, lethal dose 50; EMCDDA, The European Monitoring Centre for Drugs and Drug Addiction; Euro-DEN, European Drug Emergencies Network; GHB, gamma-hydroxybutyric acid; JWH-018, 1-pentyl-3-(1-naphthoyl) indole; JWH-0731-butyl-3-(1-naphthoyl) indole; JWH-081, 1-Pentyl-3-[1-(4-methoxynaphthoyl)] indole; JWH-122, (4-methyl-1-naphthyl)-(1-pentylindol-3-yl) methanone; JWH-210, 4-ethylnaphthalen-1-yl (1-pentyl-1H-indol-3-yl) methanone; MAM-2201, AM-2201; MBDB, beta-keto-N-methylbenzodioxolylpropylamine; mCPP, 1-(3-Chlorophenyl) piperazine; MDAI, 5,6-methylenedioxy-2-aminoindane; MDMA, 3,4-methylenedioxymethamphetamine; MDMB-CHMICA, methyl 2-[[1-(cyclohexylmethyl)-1H-indole-3-carbonyl] amino]-3,3-dimethylbutanoate; MDPBP, (1-(3,4-methylenedioxyphenyl)-2-(1-pyrrolidinyl)-1-butanone); MDPV, methylenedioxypropylvalerone; MMAI, 5-methoxy-6-methyl-2-aminoindane; MMWR, MMWR Surveill Summ; MT-45, 1-cyclohexyl-4-(1,2-diphenylethyl)-piperazine dihydrochloride; NMDA, N-methyl-D-aspartate receptor; NPS, new psychoactive substances; NPSAD, National Programme on Substance Abuse Death; PB-22, 1-pentyl-1H-indole-3-carboxylic acid 8-quinolinyl ester; PMMA, p-methoxymethamphetamine; SOFT, Society of Forensic Toxicologists; STS-135, N-adamantyl-1-fluoropentylindole-3-carboxamide; THC, tetrahydrocannabinol; TFMP, 1-(3-trifluoromethylphenyl) piperazine; TMA-2, 2,4,6-trimethoxyamphetamine; EU, European Union; UNODC, United Nations Office on Drugs and Crime; UR-144, (1-pentylindol-3-yl)(2,2,3,3-tetramethylcyclopropyl) methanone XLR-115-fluoro-UR-144.

[☆] Please cite this article as: Soria ML. Las nuevas drogas psicoactivas: populares y peligrosas. Rev Esp Med Legal. 2018. <https://doi.org/10.1016/j.reml.2017.11.004>

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Deaths;
Toxicological data

PALABRAS CLAVE

Nuevas sustancias psicoactivas;
Efectos;
Muertes;
Datos toxicológicos

order to update the knowledge available. This report deals has two objectives. The first one is to focus on the toxicological effects and health risks linked to the use of NPS. The second one is to provide information for forensic toxicologists in cases where an NPS has been identified and may have been involved in the cause of death.

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Las nuevas drogas psicoactivas: populares y peligrosas

Resumen La popularidad de las nuevas sustancias psicoactivas (NPS) se ha incrementado a pesar del posible riesgo asociado a su uso. Ante un perfil sin precedentes, la puesta en común de datos toxicológicos es vital para entender los daños asociados al consumo, y disponer de revisiones bibliográficas constituye una importante herramienta para mantener un conocimiento actualizado. Esta revisión se ha enfocado hacia los efectos tóxicos y el riesgo para la salud, así como a proporcionar datos toxicológicos forenses sobre casos en que alguna NPS haya sido identificada y relacionada con la muerte.

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Introduction

New psychoactive substances (NPS) are characterised by geographic heterogeneity, their transient nature and other characteristics that do not meet the criteria required by international control, although many of them have been associated with hospital admissions and death.¹

Notifications from the EU Early Warning System on NPS report that, in 2016, the frequency of detection was at the rate of one per week, and that the total number of new detections (66) was lower than in previous years (101 in 2014 and 98 in 2015). The data for 2017 not only do not point to a reduction in their availability, but they also talk of an increase in use among consumer populations, especially addicts and the marginalised.^{2,3}

The fact that they are easy to access on the internet—especially on the “*surface web*” or in the “*darknet markets*” and “*cryptomarkets*”, where they are sold under their own name or falsely as illegal drugs^{1,4}—as well as the profile that characterises them—low-priced, variable and quick to appear—make them popular and dangerous substances. Indeed, they are considered a daunting public health problem in both extension and complexity.⁵

New substances mean new toxicological risks for different organs, new analytical challenges in identifying them and new questions for emergency physicians and toxicologists about the therapies to carry out for adverse reactions to their consumption and overdose⁶ and to determine their potential implication in forensic cases.⁷

Due to the characteristics of the phenomenon of NPS, especially the speed with which they appear on/disappear from the market, it is worthwhile sharing current data about specific aspects of NPS with the scientific community.

In this review, the toxic effects which reveal the health risk involving consumption and forensic toxicological aspects of post-mortem cases are presented, by providing the

concentrations found for which toxicological investigations have to be carried out.

With these objectives, studies published since 2010 related to synthetic cannabinoids, synthetic cathinones, piperazines, phenethylamines and tryptamines, aminoidanes and any reference to plants with psychoactive effects have been reviewed, with the articles that present differential data on these compounds in relation to the two objectives of the review being chosen.

Toxic effects and health risk

For several years, we have experienced a period of under-declaration of the damage NPS can do to health, due to lack of knowledge about the specific effects consumers present with and the limited availability of analytically-verified data.⁸

Not being able to establish the relationship between the NPS consumed and the effect it has,⁹ has made it difficult to carry out assessments of the risk that these substances pose to health. However, the current state of knowledge leaves no room for doubt that NPS pose serious health risks.¹⁰

As well as the more well-known characteristics, others related to the profile of these substances motivate their consumption and contribute to an increased risk. Among them we can cite:

- *Seeking similar effects to those of controlled drugs in a “non-illegal” manner.* As an example, refer to the consumption of “Bromo-DRAGONFLY” (tryptamine substitute). Seeking LSD-type hallucinogen effects, we find a highly toxic NPS with a wide variety of doses on the market, which leads to a high risk of overdose. Intoxication manifests as convulsions, acidosis, pulmonary oedema and vasospasms which can result in gangrene and multi-organ failure.¹¹

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