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REVIEW

New psychoactive substances: Popular and dangerous☆

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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

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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-ADBINACA, N-1-naphthalenyl-1-pentyl-1H-indole-3-carboxamide; 5F-AMB, (S)-methyl2-(1-(5-fluoropentyl)-1H-indazole-3-carboxamido)-3-methylbutanoate; 5F-PB-22, Quinolin-8-yl 1-pentyfluoro-1H-indole-3-8-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-(cyclohexylmethyl)-1H-indole-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-PVPalpha-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, methylenedioxypyrovalerone; 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; TFMPP, 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.

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Deaths;
Toxicological data

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.

PALABRAS CLAVE
Nuevas sustancias psicoactivas;
Efectos;
Muertes;
Datos toxicológicos

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.

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 overdose[6] 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, aminoindanes 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 underdeclaration 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]

- *Seeking swift effects*. This is the case for Krokodil (desomorphine). The fact that the process of obtaining the substance is simple, along with high availability and low cost, shapes the process of self-sufficiency of consumers.[12] The speed with which it takes effect and duration of the effects means that home-made preparation to avoid withdrawal is frequent. This involves obtaining many impurities (petrol, lead, iodine, phosphorus or hydrochloric acid) that cause skin irritation, ulcers with a grey-green colour like the skin of a crocodile, and that can cause inflammation, abscesses and gangrenous areas with limb amputation.[13]
- *Lack of knowledge about what is being consumed*. As in the first case, the danger of overdose is high, either because low doses can be highly toxic, as happens with NBOMe, or because of the marked difference in toxicity among very similar compounds, such as the use of 2C-P (6–10 mg dose) instead of the less potent 2C-B (12–24 mg dose).[14]

Classified by group, considerations about the toxic effects can be summed up as follows:

Synthetic cannabinoids

Several hundred compounds belonging to at least 14 different chemical families are known about, with completely different structures from each other and THC, regarding which they also have different metabolisms and sometimes much greater toxicity. Also among these, different modifications of their molecules have increased their toxicity, although only occasionally is this variation quantified. We can cite the case of JWH-018, whose mechanism of decreasing neurotransmitter release is 10 times lower than AM-2201, which is structurally related.[15]

The changing pathway of these compounds has led to so-called second-generation compounds (UR-144 and XLR-11), with much higher toxicity and, more recently, to third-generation compounds (5F-ADBINACA, AB-FUBINACA and STS-135). Studies on the latter reinforce the hypothesis of their harmful effects on human health with initial impairment of the sensory-motor response and later of motor activity. At high doses, they induce severe neurological effects (convulsions, myoclonus and hyperreflexia) and provoke aggression.[16,17]

Without distinguishing between them and according to data provided by the MMWR in 2015, the most common adverse effects are agitation (35.3%), tachycardia (29%), dizziness and drowsiness (26.3%), vomiting (16.4%) and confusion (4.2%),[18] which coincides with the results from 51 articles with more than 200 cases of acute intoxication in those presenting with symptoms of agitation or irritability, fatigue, anxiety, confusion, short-term cognitive and memory impairment and psychosis. Some cases result in prolonged psychiatric effects, paranoia, mental disorders and suicide attempts.[19] Other reviews indicate that clinical symptoms disappear on average 6 h after use,[20] not lasting more than 8 h.[21]

Such manifestations vary depending on dose, route of exposure and the agent involved, but patients generally experience profound stimulating effects compared with traditional marijuana consumption. For some patients, severe withdrawal symptoms are also apparent and there are reported cases of death.[22–28]

Synthetic cathinones

The main reasons justifying the meteoric increase in their popularity are the ease of synthesis from common and legal precursors, which reduces the price, as well as a profile reminiscent of cocaine, of ecstasy and of hallucinogenic piperidines.[29]

The clinical symptoms are tachycardia, hypertension, chest pain and muscular contractions.[30] Intoxicated patients may present with extreme sympathetic stimulation and may experience a deeply affected mental state with panic attacks, agitation, paranoia, hallucinations and violent behaviour, such as self-mutilation, suicide attempts and murderous activities.[31]

They are rapidly absorbed orally, the maximum peak being reached after 1.5 h. In general, symptoms of intoxication may last between 1 and 6 h, but the ''comedown'' may last up to 2 days.[32]

Structural modifications translate into different mechanisms of action; therefore, mephedrone has an extremely powerful effect on serotonin and dopamine transporters and a weak effect on the monoamine transporter, while the pyrrolidine ring of MDPV is responsible for the effect of blocking the dopamine and norepinephrine transporters.

The increase in dopamine is sometimes up to tenfold. For this reason, authors like Karch[33] have associated them with excited delirium. One of the foundations of this situation is produced when the reuptake of dopamine is blocked, and it remains in the synaptic space. As a consequence, aggressive behaviour, delirium, agitation and sudden death develop when the neurocardiac axis is activated.

The physical manifestations of intoxication include tachycardia, hypertension, vasoconstriction, arrhythmia, hyperthermia, tremor, convulsions and hyperreflexia, in some cases rhabdomyolysis, stroke, myocardial infarction, disseminated intravascular coagulation, respiratory failure, coma and death. The psychological manifestations of anxiety, agitation, paranoia, hallucinations, aggressive and violent behaviour, delirium and suicidal thoughts can be profound after just one dose of the drug. The long-term neurological effects are unknown.[34]

Piperazines

The manifestations of their consumption are characterised by an increase in blood pressure and heart rate, accompanied by an increase in euphoria, dysphoria and sociability. Psychological problems such as loss of energy, mood swings, confusion and irritability also arise.[35]

BZP itself is a stimulant of the central nervous system, with a potency equivalent to 10% of d-amphetamine, which stimulates the release of dopamine, noradrenaline and serotonin and also inhibits their reabsorption, simulating the effects of amphetamine. Concentrations of up to 0.5 mg/l are associated with anxiety, vomiting and palpitations, and, above this value, with agitation and confusion. Convulsions may arise with very low concentrations, but regularly

correspond to concentrations of around 2000 mg/l.[11] The studies carried out reflect that they have a narrow safety margin and the neurotoxic effects manifest as brain dysfunction as a result of their neurodegenerative properties.[36]

Phenethylamines (2C-x)

These cause psychedelic and hallucinogenic activity due to the inclusion of a 2-Methoxybenzyl in the nitrogen of the 2C-x which leads to hallucinogenic activity, even in the order of micrograms, presenting itself as an alternative to LSD. The clinical picture presents both stimulating and hallucinogenic effects and the signs and symptoms include nausea, vomiting, dizziness, diarrhoea, headache, body pain, depression and confusion.[37]

As in other groups, the consumption of different compounds from the same family may have different consequences. An example is the case of 2 CB or 4 FA and benzofurans (5-6APB), which present the same mechanism of action and some common effects; however 2 CB and benzofurans provoke a severe psychological effect with hallucinations and psychosis that has not been reported for 4 FA, and, while 5-6APB has been linked to at least 10 deaths, only one has been linked to 4 FA and none for 2C-B.[10]

Tryptamines

These are derivatives of 2C phenethylamines and at least seven varieties are known about, popularly known as NBOM. Their activity at extremely low doses, lack of knowledge about the LD50s and poly-drug use contribute to the risk of accidental overdose which may cause death, either directly due to its own effects, or indirectly due to the behavioural disorders and resultant effects of traumatic injuries.[38]

The toxicity of these compounds may present as hallucinations, agitation and severe medical complications.[39] The ''Personal drug experience websites'' describe a ''medium high'', with peaks of euphoria and a tingling sensation. The sensation of stimulation is ''unique'', and is described as energetic and at the same time devoid of any movement, at least intentionally. In some cases, stimulation is uncontrolled, with agitation in the body and chattering teeth comparable to that produced by MDMA and amphetamine. Other effects come into play as the dose increases, with depersonalisation, anxiety, disassociation, panic and fear, described as ''something terrifying to the body''.

Aminoindanes (MMAI, MDAI and 5-IAI)

These affect the 5-HT system and inhibit the synaptosomal reuptake of serotonin, dopamine and noradrenaline, with this being the key to their popularity. Their effects are occasionally unexpected and may be due to concomitant consumption with other drugs such as cocaine, amphetamine and methamphetamine.[40]

Lastly, and in reference to the number of known plants that cause psychoactivity, the hallucinogenic properties of fungi, known about for millennia should be mentioned, or the stimulant properties of Khat, similar to amphetamines: it induces psychosis and has cardiovascular effects, although somatic and mental problems have not been completely described. Others, such as Kratom, Kava or Betel, have stimulating effects, and *Salvia divinorum*, Lysergamides, Ayahuasca, Bufotenin and Ibogaine have hallucinogenic effects.[41]

Currently it is considered necessary to prioritise substances that are more harmful, persistent and prevalent, for which the partnership between the United Nations Office on Drugs and Crime (UNODC) and The International Association of Forensic Toxicologists (TIAFT) has been launched in order to meet, and analyse and share toxicological data at a global level, and strengthen the ability to make decisions based on scientific evidence.[1]

Forensic toxicological aspects

As in the case reports, in those in which death may be related to NPS, the detection and identification of the substance(s) concerned poses a challenge for laboratories. In some cases, indications about the type of consumption start from the confession of the patient him/herself or the people accompanying him or her, or who were present at the act; however, the presence of the causative compound has to be confirmed by reliable analytical methods.[6,42]

The growing number of new compounds, at an unprecedented rate, requires a rapid and permanent update of the analytical methods in clinical and forensic laboratories.[43]

For new compounds, taking into account the ineffectiveness of most of the methods available for toxicological screening of NPS in biological samples,[44,45] as well as the lack of knowledge about the metabolic patterns that follow, there is a possibility that the implicated compound will not be identified,[46] or that the result will be inconclusive.

However, there are currently numerous publications available on analytical methods and concrete cases where death is linked to these substances, which provided toxicological forensic data of interest when we interpreted our results.

With this intention, the data on cases of death linked to the consumption of NPS since 2010 were reviewed and are presented in chronological order.

One of the first structural modifications in illegal laboratories for recreational purposes were on the amphetamine molecule, and deaths associated with the consumption of these compounds soon occurred. The first of these, associated with PMMA, was in Spain (1993). Subsequently, three cases were reported in Denmark, one in Germany in 2003, eight in Taiwan in 2006, 24 in Israel between 2008 and 2009 and 12 in Norway in 2010 and 2011. Its presence was identified in all cases, although it could not be concluded as the cause of death in any case.[47]

In the case of synthetic cathinones, the first deaths related to mephedrone (2009) occurred in Scotland and England, with four cases with concentrations between 1.2 and 22 ng/l.[48] Previously, another case had been reported in Sweden in 2008, in which mephedrone was detected exclusively.

Following the first data on consumption in the United States,[49] in 2011 deaths due to MDPV and methylone (56 ng/ml and 735 ng/ml, respectively) were published, in the first review in which the type of case and the con-

centrations found were provided. There was an overlap of concentrations for living and deceased individuals, signalling that death may be linked to consumption, although other compounds were detected.[50]

Maskell et al.[51] compiled four cases of death by mephedrone on top of what had been published up until then. Concentrations found varied between 0.13 and 2.24 mg/l, referring to other cases with concentrations between 22 and 33 mg/l, and four cases of death related to MDPV were reported in Poland, which were published in 2013.

In 2012, data from the NPSAD reported that the prevalence of NPS had increased by 800% in three years, from 12 in 2009 to 97 in 2012, and that the number of cases of related deaths had increased by 600%, from 10 cases in 2009 to 68 in 2012.[52] The first references to deaths due to synthetic cannabinoids appeared, with results from 18 different cases being revealed. All the blood samples analysed contained JWH-018 in concentrations between 0.1 and 199 ng/ml, and eight of these also contained JWH-073 between 0.1 and 68 ng/ml.[53]

In that year, Vevelstad et al.[54] reported 34 cases in which PMMA was detected and, of those, 12 were post-mortem. In these cases, the mean concentrations in peripheral blood were 1.92 mg/l (0.17–3.30 mg/l), and 0.10 mg/l (0.01–0.65 mg/l) in living individuals.

In 2013, numerous cases of death linked to cathinones were published. We note data from four cases of death due to methylone, with concentrations in the blood of 0.740, 0.118, 0.06 and 1.12 mg/l.[55]

Marinetti and Antonides[56] compiled the results from 32 cases related to NPS, of which 23 were post-mortem. MDPV, methylone, pyrovalerone, pentylone, α-PVP and mephedrone appeared in all of them. The most frequent was MDPV, with concentrations of between 10 and 640 ng/ml in post-mortem cases, overlapping with concentrations found in living individuals (<10 to 368 ng/ml).

Another two articles reported three deaths with MDPV, two of which had concentrations of MDPV of 0.039 and 0.130 mg/l in femoral blood; however, these deaths were attributed to natural causes.[57] In other reported cases, the concentrations in the blood were 306, 124 and 17 ng/ml, although its presence was not unique.[58] In later studies, the concentrations found in drivers were 0.030 mg/l[59] or ranged between 0.01 and 0.30 mg/kg.[60]

With regard to cases of death due to synthetic cannabinoids, Kronstrand et al.[61] quantified 14 different compounds in blood samples from 862 forensic cases. For eight of them (AM-694, AM-2201, JWH-018, JWH-081, JWH-122, JWH-210, MAM-2201 and UR-144) a mean lower than 0.5 ng/g was found, a concentration in the order of those reported by Yeakel and Logan[62] (12 cases). These authors had studied the influence of these compounds: JWH-018, JWH-250, AM-2201, JWH081, JWH-122 and JWH-210 in drivers, finding concentrations of between 0.1 and 9.9 ng/ml. In monographs for some of them, such as AH-7921, the post-mortem values were between 0.08 and 0.99 μg/g in femoral blood.[63]

Seetohul and Pounder[64] reported four cases of death attributed to 5-IT (substituted indole) with stimulant properties. Concentrations in cardiac and femoral blood in the four cases were: (1) 1.2 and 0.8; (2) 2.6 and 0.9; (3) 0.8 and 0.4; (4) 0.4 and 0.3 mg/l.

In 2014, numerous press articles were published with titles such as ''New figures reveal legal high drug deaths more than doubled in last year'' in 'The Herald' (Scotland) or ''Legal Highs Killing More People in the UK'' on the IBTimes page and BBC News, which also includes the United Nations study showing that 670,000 young people in the United Kingdom were using NPS with an increase in deaths from 10 in 2009 to 68 in 2012.

The scientific publications described four cases of death due to 5F-PB-22 with concentrations of between 1.1 and 1.5 ng/ml, in post-mortem blood samples,[23] and the first data appeared on deaths due to 25I-NBOMe with concentrations in peripheral blood of 405 pg/ml and 410 pg/ml in cardiac blood.[65] Similarly, the first deaths were reported due to 4,4′-DMAR (18 cases), with concentrations found of between 0.20 and 3.75 mg/l (mean 1.18 mg/l), although other drugs played a role in all of these cases.[66]

That year, suicides with cathinones were reported with a wide range of concentrations which, as in previous cases, overlapped with those of living individuals. As an example, we cite the case of mephedrone, with concentrations of between 0.15 and 3.09 mg/l, while concentrations of 0.02–2.23 mg/l are found when it is not a cause of death.[67]

At the end of 2014, the cannabinoid MDMB-CHMICA was detected in nine autopsies in Sweden, and, in at least two of these, it was the cause of death. During 2014 and 2015, this compound had also been linked to deaths and cases of serious toxicity in Germany, Poland and the United Kingdom.[68]

In 2015, results were published on AB-CHMINACA, 5F-AMB in post-mortem adipose tissue,[69] of 5F-ADBINACA at a concentration of 0.64 ng/ml,[70] and the first death due to 5F-AMB was reported, with a concentration in the blood of 0.3 ng/ml.[26]

Other cases of death were those reported due to the combination of pentedrone, α-PVP and its metabolite 1-phenyl-2-(pyrrolidin-1-yl) pentan-1-ol (OH-a-PVP) at concentrations of 8.79, 901 and 185 ng/ml, respectively.[71]

With regard to 25I-NBOMe, we refer to the case in which a significantly high concentration, of 28 mg/l[72] was found, along with synthetic cannabis XLR-11 at a concentration of 1.4 ng/ml. The authors draw attention to the fact that in case reports the concentrations became between 23 and 60 times higher.[16] Other deaths due to 25H-NBOMe and 25C-NBOMe had concentrations of 1 and 0.7 mg/l, respectively,[73] and of 1.59 ng/ml for 25B-NBOMe and of 19.8 ng/ml for 25I-NBOMe in other cases.[74]

Lee et al.[75] reported nine deaths related to ethylone; seven of those had concentrations of between 38 and 2.57 ng/ml. McIntyre et al.[76] reported a case of death due to 4-methoxyphencyclidine and 4-hydroxy-N-methyl-N-ethyltryptamine, with a concentration in peripheral blood of 8.2 mg/l. They were unable to quantify the second compound.

We also note a case in which 3,4-dimethylmethcathinone was found, at a concentration of 3.31 μg/ml in the blood,[77] and deaths that were compiled in reviews such as the publication by Chung et al.[78] related to synthetic cannabinoids such as JWH-018, JWH-073, AM-2201, cathinones such as MDPV, mephedrone, methylone, α-PVP, PV9, with 25I-NBOMe, PMMA and methoxetamine.

In 2016, regarding compounds related to cathinone, 3 MMC was detected in post-mortem blood at a concentration of 0.33 mg/ml, although the presence of GHB was also detected.[79]

With regard to mephedrone, it was determined as the cause of two fatalities with very similar concentrations: 0.173 and 0.170 mg/ml.[80] These results are in line with two studies from 2017, where a concentration of 0.249 mg/ml[81] was found, and in the order of those found in a suicide case with methylone (0.936 mg/ml) and mephedrone (116 mg/ml).[82]

In the cases of death due to MDPBP, the concentrations were 1.55, 7.01 and 9.32 μg/ml,[83] and another case of death due to methylone was referenced with concentrations of 0.5 mg/ml, although other compounds were found in the deceased.[84]

We note that, although mephedrone is perhaps one of the best known NPS, there are still no studies linking doses with concentrations in the blood.[85]

Regarding synthetic cannabinoids, we can refer to the case of a death due to AB-CHMINACA concomitantly consumed with alcohol, in which there were concentrations of between 0.1 and 2.7 ng/ml in blood samples from different areas, a case that is compared to the first case, reported in 2015, and in which, although the compound was found in several samples, it was negative in the blood.[27]

In 2017, the comparison of three situations in which α-PVP had been detected were reported. One case of death by hanging with a concentration of 12 ng/ml, the peripheral blood of a driver with 120 ng/ml and an intoxication with 174 ng/ml in the post-mortem blood, with data provided from other biological fluids.[86] Regarding this same compound, we refer to a review of 21 cases with post-mortem concentrations of between 0.033, 0.054 and >20 mg/l, in one case in the order of the mean found in 18 drivers, of 0.030 mg/l.[87]

The consumption of cathinones is considered worrying. Cases of suicides with methylone (936 ng/ml) and mephedrone (116 ng/ml)[88] have been reported, and second-generation compounds derived from α-pyrrolidinophenone have been identified as causing intoxication and death, in some cases also related to suicide. The main compound involved was α-PVP (200 cases including 105 deaths, up to 2015), with concentrations of up to 6200 ng/ml,[89] and MDPV, with high variability, from traces (<10 ng/ml) up to 576 ng/ml. In almost all of these, there was poly-drug use with other cathinones and illicit drugs.[90]

We note the review by Kubo et al.,[91] in which 84 cases of death were compiled (2010–2016) with 33 different NPS, of which 45% were acute intoxications, and the publication by Karinen and Høiseth[92] on concentrations of phenethylamines, aminoindanes, arylalkylamines, arylcyclohexylamines and indolealkylamines, all of which are stimulants. In this review, even with a wide range of concentrations, the impression given is that NBOMe drugs are detected at low concentrations, and, although it is difficult to come to any conclusions, it may indicate that they are highly potent and that low doses may cause symptoms of intoxication.

Regarding synthetic cannabinoids, in the literature consulted in 2017, no deaths caused by these compounds were described, although we have to point out the murder committed by an individual who had consumed AM-2201 and THC between 1 and 1.5 h beforehand, found at a blood concentration of 0.48 ng/ml and 23 ng/ml, respectively.[28]

Intoxication and death due to synthetic opiates, especially fentanyl and its derivatives, also considered NPS, have been reported and qualified as an ''epidemic''. In fact, the latest UNODC report indicates that the greatest percentage increase in consumption has been detected in synthetic opiates, which represented 2% in 2014 and 4% in December 2016.[93]

Conclusions

The popularity of consumption of these substances poses a risk to the health of individuals consuming them and continues to pose a challenge for clinical and forensic laboratories.[94]

However, the answers provided by research studies, beyond basic pharmacology, are playing a key role in understanding the acute and long-term effects of NPS.

From the studies compiled for this review, the following conclusions can be drawn:

- The fact that the vast majority of NPS are legal and easy to access, and lack of knowledge about the risks, contribute to their popularity and dangerousness.
- The consumption and frequent poly-consumption of NPS result in death, suicide, serious injury and adverse effects on health. Their long-term effects are currently unknown.
- It is difficult to establish toxic and lethal concentrations, with there being an overlap between concentrations found in living and deceased individuals. In many cases, very low concentrations are capable of producing intoxication and death.

While this last point is known for the classic drugs, for these it was concluded after many studies, and they are needed for NPS.[7]

Regarding future trends, the difficulty experienced with analytical determinations has led to the suggestion that in routine forensic analysis, unambiguous identification would be sufficient and would give us a more realistic, global vision of the situation we currently find ourselves in.[1,7]

It also proposes establishing a ''minimum required operating limit'', being the minimum concentration of an analyte in the sample, which could at least be detected and confirmed. This could be applied to other areas of forensic toxicology, like chemical submission, and would level out the degree of quality for the laboratories that defend these cases before the judges and courts.[95]

Conflicts of interest

The author declares that she has no conflicts of interest.

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