Toxicological findings in fatal intoxications from synthetic cathinones: a narrative review

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ABSTRACT
Since description of autopsy findings and an indication of fatal concentrations related to overdoses from synthetic cathinones are rare, we reviewed the literature using three different search engines including articles from 2010 to 2019. Fifty-two resulted in line with our inclusion criteria providing information about 142 subjects, treated as individual cases. From our analysis most cathinones related deaths derived from polydrug abuse. In very few cases, death could be ascribed exclusively to the use of synthetic cathinones, namely mephedrone (4-MMC), butylene (Bk-MBDB), methylone, α-pyrrolidinopentiophenone (α-PVP), 3,4-dimethylmethcathinone (3,4-DMMC), 3',4'-Methylenedioxy-α-pyrrolidinobutiophenone (MDPBP), α-propyl-loaminopentiophenone (N-PP), 4-methylmethcathinone (4-MEC) and 4'-methyl-α-pyrrolidinohexiophenone (MPHP), with blood concentrations generally higher than 0.5 mg/l in blood. Toxicological knowledge of these substances remains scarce and any contribution would prove fundamental in reconstructing their toxicity profile.

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Introduction
From khat to synthetic cathinones
For centuries, chewing khat leaves, for its stimulating effects, has represented a tradition in different communities\(^1\). Because of its known properties, the plant was studied from the beginning of the century, with the synthesis of new molecules, initially created for therapeutic purposes, now part of the group of synthetic cathinones\(^2,3\), a new category of psychoactive drugs NPS or ‘legal highs’ commonly sold as ‘bath salts’, in the United States, or ‘plant feeders’ or ‘plant food’, term most often used in Europe. Although they are sold as products labelled with warnings ‘not intended for human consumption’ or ‘not tested for risks or toxicity’, these drugs are intended to produce a psychic effect similar to that

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obtained with illegal stimulants, such as methamphetamine, MDMA (ecstasy) or cocaine. Cathinones are easily available online, on websites and smart shop, marketed as cheap and apparently safe products, capable of generating the same effects of the most known drugs. Online stores are, in fact, famous for their flexibility and rapid adaptation to changes of psychoactive substances legal status, as well as to the needs of consumers.

The names of these products can be fictitious or evoke substances whose effects they intend to mimic. Among the most common we find ‘Meow Meow’, ‘Kitty’, ‘Flakka’, ‘Cloud Nine’, ‘Lunar Wave’, ‘White Fulmine’, ‘Bloom’, ‘Scarface’ ‘Vanilla Sky’, ‘Coco Power’, ‘Crack Inside’, ‘EXTC’, ‘Xtacy’, ‘Dynamite’, ‘Euphoria’, ‘Explosion’, ‘Loved Up’, ‘Mind Candy’, ‘Rocket Fuel’, ‘Sextasy’, ‘Torpedo’ generally available in the form of odourless, white, yellowish or brown powders and crystals, more rarely in the form of tablets or capsules, and sold in transparent plastic bags.

**Chemical structure**

Despite their similar structure, synthetic cathinones can be chemically organized into four groups (Figure 1): 

(A) ‘Classic’ cathinones – consisting of a substituted or unsubstituted benzene ring and a side chain. Examples of these cathinones are mephedrone or buphedrone. 

(B) Pyrrolidinopropiophenone derivatives – consisting of a benzene ring, substituted or not substituted, and a pyrrolidinyl ring on the side chain. This is the case for substances such as methyl-α-pyrrolidinopropiophenone (MPPP) or MPBP. 

(C) The ‘3,4-methylenedioxy–N-Alkylated’ cathinones – are composed of a 3,4-methylenedioxyphenyl ring and a side chain, for example, methylone, butylone and pencylone, molecules very similar to MDMA. 

(D) ‘3,4-methylenedioxyphenyl-N-pyrrolidine’cathinones. It is the model of MDPV, 3,4-methylenedioxy-α-pyrrolidinopropiophenone (MDPPP) and MDPBP.

**Method of consumption**

The most common means of consumption of for synthetic cathinones are sniffing, oral ingestion of capsules or tablets, dilution with water or fruit juice, or ingestion of paper-wrapped powder, to carry out the so-called ‘Bombing’. Cases of intravenous, subcutaneous, intramuscular, or rectal use have been reported in the literature. There have also been reports of ocular absorption, so-called ‘eyeballing’. Information regarding effective doses and time of action is available only for very few molecules, for which studies have been carried out on rats; scarce information derives from cases of intoxication while most of the data are mainly derived from surveys conducted on the Internet, and mainly concern the synthetic cathinones that have experienced the greatest diffusion such as mephedrone and MDPV. According to the questionnaires, mephedrone is generally taken in sessions lasting up to 10 h, a period of time in which a dose of substance equal to 0.5–1 g is taken, divided into several doses.

For sniffing, doses ranging from 25 to 75 mg are used, with rapid and short-lasting effects that occur in a few minutes and last less than an hour.
Oral doses of the substance are 150 and 250 mg, with a latency of action ranging from 45 min to 2 h, and effects that last for 2–4 h. Several consumers first snort and then ingest the substance in order to achieve both fast and long-lasting effects.

Whit regards to MDPV, the literature indicates that the effects sought occurred with a dose of 3–5 mg and that the average dose varies from 5 to 20 mg. The risk of overdose is
C) 3,4-methylenedioxy-N-alkylated cathinones

Figure 1. (Continued).
high, since the substance is sold in bags that usually contain up to 500 mg bearing labels that suggest taking doses of up to 50 mg. Within 60–90 min, the drug begins to give the desired effects that last for 6–8 h. Data in the literature suggest that these substances are taken in combinations with other drugs in order to reduce the side effects or to improve the desired ones. In fact synthetic cathinones can be consumed with alcohol, propranolol or another β-blocker to counter tachycardia; with cannabis and diazepam or alprazolam to counteract anxiety and over stimulation; famotidine, omeprazole or domperidone to counter gastritis; other psychostimulants such as cocaine, amphetamine, modafinil, trifluoromethylphenylpiperazine, benzylpiperazine, butylone, methylone or pentylone to enhance the stimulating effect; opiates such as morphine or tramadol to create ‘speedball’; ketamine or zopiclone to improve the phenomena of visual hallucinations.

Pharmacokinetics and pharmacodynamics

At present, knowledge of the pharmacokinetic and pharmacodynamic effects of these substances is very limited. Information on this topic derives mainly from reports on the Internet. The absorption of these substances depends on the route of intake and is delayed in the presence of food in the stomach, with a later onset of effects when taken after a meal. Additional data in the literature were acquired through gas chromatography/mass spectrometry methods in rats and humans. These studies have shown that synthetic cathinones can be metabolized by several pathways, which vary according to their molecular structure. For the so-called classical cathinones, such as mephedrone, studies on metabolism in humans and in rats have shown that the enzyme responsible for phase I metabolism in vitro is the cytochrome P450 2D6 (CYP2D6), with some minor contributions by other NAPDH-dependent enzymes. In four cases of forensic interest in which mephedrone was detected, several metabolites were identified in the blood: hydroxytolyl-mephedrone and dihydromephedrone, norephedrone, dihydro- mephedrone and 4-carboxy-mephedrone. In one case, the analysis of a urinary sample revealed the presence of hydroxoytolyl-mephedrone, norephetone, dihydromorphine- drone, 4-carboxy-mephedrone and 4-carboxy-dihydromes-drone.
Studies on ‘3,4-methylenedioxy’ cathinones such as the methylene or butylene which have the β-keto group and the methylenedioxy group have suggested that their main urinary metabolites (4-hydroxy-3-methoxymetcatinol-4’-OH – 3’-MeO or HMMC) and 3-hydroxy-4-methoxymetcatinol (3’-OH-4’-MeO) are produced by demethylenation followed by O-methylation of the hydroxyl group on the benzene ring. Their major metabolite is represented by the HMMC, both in rats and in humans, therefore its analysis can become useful to demonstrate the consumption of these substances. Another metabolic pathway, although minor is N-dealkylation in a primary amine.

For the last group of cathinones, a screening study found that cytochrome P450 isoenzymes CYP2C19, CYP2D6 and CYP1A2 are capable of catalysing demethylenation in vitro. The resulting molecule is then subjected to COMT action, and transformed into methylcatecol and pyrrolidine, in turn glucuronidated, to promote renal excretion.

Information about the mechanism of action of these new drugs is also scarce, but due to their structural similarity with amphetamine derivatives, it is believed that they act in a similar manner. Scientific evidence supports this hypothesis indicating that cathinones, such as amphetamines, interact with dopamine (DA), norepinephrine (NA) and serotonin (5-HT) membrane transporters leading to an increase of synaptic concentrations of these biogenic amines. Gonçalves et al. in his review referring to the study of Simmler et al. classified synthetic cathinones into three major groups in order to summarize their mechanism of action. According to their studies, the ‘cocaine-MDMA-mixed cathinone’ group including mephedrone, methylene, ethylene, butylene, and naphyrone shows non-selective inhibition of monoamine reuptake, with an affinity for DA transporter higher than that for 5-HT transporter, also inducing the release of 5-HT in a manner similar to MDMA. The second group, indicated as ‘methamphetamine-like cathinones’, includes cathinones that act as preferential catecholamine (DA and NA) reuptake inhibitors and DA releasers, with greater inhibition on DA and low on 5-HT transporters. ‘Pyraleronone-cathinones’ are the third group, being characterized by very potent and selective inhibitors of the catecholamine reuptake, which do not promote the release of neurotransmitters.

**Effects**

As it is possible to deduce from their pharmacodynamics, synthetic cathinones consumption determines psychorganic alterations related to their stimulating effect. Also, data concerning the desired effects are based on self-reports, collected through questionnaires and retrospective surveys, with poor qualitative and quantitative toxicological information. These data should therefore be considered with caution, as not completely reliable. People who used synthetic cathinones have frequently compared their effects with those exerted by cocaine, amphetamine and MDMA, with increased attention and awareness, greater energy and motivation, euphoria, excitement, positive effects on mood, empathogen effects, openness in communication, sociability and talkativeness, intensification of sensory experiences, moderate sexual arousal and perceptual distortions, reduced appetite and insomnia. Mephedrone effects are described by those who use it as more similar to those of MDMA than those induced by cocaine.

The negative effects of synthetic cathinones include a wide range of symptoms which can be divided into the following main groups:
Cardiovascular symptoms: tachycardia, palpitations, chest pain, hypertension, changes in the S-T segment, myocarditis, cardiac arrest.

Neurological symptoms: confusion, cognitive impairment, mental fatigue, disorientation.

Psychiatric symptoms: aggression, violent or even criminal behaviour, anxiety, panic attacks, lack of motivation, anhedonia, depression, suicidal thoughts.

**Main methods of toxicological analysis**

These substances are not easily detected because their toxicological analysis represents a significant challenge for forensic laboratories. The speed with which new drugs are introduced can significantly exceed the ability of many forensic toxicology laboratories to develop and validate analytical methods. Furthermore, many of the newer substances are not easily detectable with traditional methods of screening and confirmation and may require complicated and expensive instrumental techniques. Immunological screening has not proven effective for the large number of drugs within the class of synthetic cathinones and cross-reactivity with antibodies to amphetamine has been noted. In addition, cathinones undergo a variety of phase I transformations including N-dealkylation, reduction, hydroxylation, oxidation and demethylation and despite constant scientific progress, metabolite standards are commercially available only for a relatively small number of cathinones. For this reason, most methods tend to search for the primary substance. This approach has proven effective due to a sufficiently high concentration of the parent substance present in biological samples. Chromatography Coupled with Mass Spectrophotometer (GC-MS) is the most widely used technique in the field of forensic toxicology, due to its great reliability and relatively low costs compared to other methods. However, it has been noted that synthetic cathinones can undergo thermal degradation during gas chromatographic analysis. Noggle and De Ruiter were the first to document this phenomenon in 1994 by analysing methcathinone. Archer and Tsujikawa observed a similar result, like L. Glicksbergand S. Kerrigan, who highlighted this type of thermal degradation in 18 synthetic cathinones. On the other hand, the approach with Liquid gas Chromatography and Mass Spectrometry (LC-MS) obtains an optimal analysis of this class of substances since the ElectroSpray Ionization conditions (ESI) can be controlled and optimized satisfactorily according to the analytes. Ammann was the first to use Liquid Chromatography – tandem with Mass Spectrometry (LC-MS/MS) to simultaneously identify a larger number of cathinones (twenty-five) in the blood. More recently, High-Resolution Mass Spectrometry (HRMS) has been used to detect cathinones in the blood and urine. Although triple quadrupole mass spectrometry is considered the most sensitive method, HRMS and Orbitrap approaches have improved mass accuracy.

There are just a few published case reports in the literature dealing with intoxication from synthetic cathinones and an even smaller number of fatal cases attributed to the use of these substances, nor is there much information on the blood concentration needed to overdose. On the basis of these premises, this narrative review of the scientific literature aims to detect fatal cases in which synthetic cathinones have contributed to the patient’s death. Furthermore, we selected and investigated cases in which death was caused by overdose by a single cathinone, in order to identify fatal concentrations of this group of drugs in blood.
Materials and methods

From January to June 2019, we performed a review of the literature using three different search engines: PUBMED, WEB OF SCIENCE and SCOPUS, including articles from 2010 to 2019. The literature research was conducted by three subjects – I.M, F.F, L.P. – using the following keywords: ‘synthetic cathinones, cathinone, death, post-mortem, bath salts, Mephedrone (4-MMC), Methylenedioxypyrovalerone (MDPV), Methylenedioxypyrovalerone, Methedrone, Methylone, Dibutylone, α-pyrrolidinopentiophenone (α-PVP), α-pyrrolidinohexiophenone (α-PHP), Ethylone, Pentedrone, α-pyrrolidinoheptaphenone (α-PV8), Buphedrone, Pentylone, Methedrone, Methcathinone, 4-methylethcathinone (4-MEC), 4′-Methyl-α-pyrrolidinoheptaphenone (MPHP), Butylone, 4-Chloromethcathinone (4-CMC), N-ethylpentylone (NEP), α-pyrrolidinoctanophenone (PV9), α-propyloaminopentiophenone (N-PP), 3,4-dimethylmethcathinone (3,4-DMMC), 3′,4′-Methylenedioxy-α-pyrrolidinobutiophenone (MDPBP)’. The inclusion criteria were

- Articles should report cases in which the use of synthetic cathinones could have contributed to the determination of death
- Autopsy
- Post-mortem toxicological analysis
- Articles should be written in English.

Statistical analysis on data was performed with STATA 16.1 (StataCorpLP, Collage Station TX, USA).

Results

The research initially produced 8,362 results, whose titles were examined first. Out of the articles examined, four were discarded because they were not written in English. Duplications and studies that were not in line with the inclusion criteria were also excluded. At the end of this preliminary phase, 133 articles were identified, whose abstracts were then analyzed; 66 articles that did not meet the inclusion criteria were excluded. The remaining 67 articles were examined in full-text form and 15 were discarded because they were not in line with our criteria. At the end of the process, 52 full-texts were thus selected and deemed suitable for our study.

Once the 52 final articles were selected, we elaborated a table in which we included the data of 142 subjects, treated as individual cases in the texts. For each of them, we indicated the circumstances and cause of death and the data from the toxicological investigations on blood. Data entered in the table are the same as those reported by the authors in their articles. The concentrations of the substances were converted where possible in ng/mL to make the data homogeneous. Supplementary Table 1 reports the main characteristics of the studies included in our review (Supplementary Tab. 1).

Most of the case studies were from the United States (36.4%) and Poland (29.5%), the remaining from other European Countries and Canada (Figure 2).
The data refer to a population made up mainly of male subjects (n.112) aged between 17 and 56 years (mean 30.3). The female sample consisted of 26 subjects aged between 17 and 55 years (mean 34.5). Sex was not indicated for four subjects.

With reference to the circumstantial data and the clinical history of the subjects, when indicated in the article, our analysis showed that 11 subjects (7.8% of the total) used synthetic cathinones during social situations, concerts or parties; in 7 (4.96%) cases violent behaviour was detected; 12 (8.51%) subjects had a history of psychiatric disease not related to drug abuse; in 9 (6.38%) cases hyperthermia was developed following the consumption of methylone, MDPV, butylone and methedrone.

Most deaths were defined by the authors as accidental (86 cases), in 14 cases as suicide, in 5 as natural, in 4 as homicide, in which death was independent from the action of drugs.

In 68 cases, death was caused by overdose following polydrug assumption.

In 17 cases, the cause of death was attributed to an overdose caused by a single synthetic cathinone, namely mephedrone, butylone, methylone, α-PVP, 3,4-DMMC, MDPBP, N-PP, 4-MEC. Tables 1 We therefore, created Table 1, to show the post-mortem toxicological data related to these cases of fatal intoxication, indicating in particular synthetic cathinones mean blood concentrations (Tables 1 and 2).

For three substances, namely, mephedrone, methylone and α-PVP it was possible to make a comparison between the mean drug blood concentrations found in cases of overdoses caused exclusively by the substance itself and those caused by a polydrug consumption. To test the equality of concentration values we used the Wilcoxon rank-sum test, which is also known as the Mann–Whitney two-sample statistic. A p-value of less than 0.05 was considered to be statistically significant. The two groups were not significantly different.

**Figure 2.** Articles countries of origin.
Table 1. Toxicological data in deaths caused exclusively by cathinone. MIN = lowest concentration found in the literature; MAX = highest concentration found in the literature. All concentrations indicated in this table relate to blood concentrations.

| Drug          | Number of cases included | MIN       | MAX       | MEAN       | REFERENCES |
|---------------|--------------------------|-----------|-----------|------------|------------|
| Mephedrone    | 3                        | 980 ng/mL | 5500 ng/mL| 3260 ng/mL | 57,58,63   |
| Methyline     | 4                        | 670 ng/mL | 840 ng/mL | 730 ng/mL  | 60,61,73,86|
| Alpha-PVP     | 4                        | 174 ng/mL | >20000 ng/mL| 5267.75 ng/mL| 67,83,95,102|
| 3,4-DMMC      | 2                        | 3310 ng/mL| 2700 ng/mL| 15155 ng/mL| 76,99      |

| Drug        | Number of cases included | CONCENTRATION     | REFERENCES |
|-------------|--------------------------|-------------------|------------|
| 4-MEC       | 1                        | 14,600 ng/mL      | 103        |
| Butylone    | 1                        | 20,000 ng/mL      | 49         |
| N-PP        | 1                        | intraday 3200 ± 680 ng/mL | 89         |
|             |                          | interday 3100 ± 23 ng/mL |           |
| MDPBP       | 1                        | 9.32 μg/cm³       | 85         |

Discussion

**Toxicological findings in cases of death caused by synthetic cathinones**

Cases of death have been described in the literature, in which forensic toxicology investigations have shown the presence of synthetic cathinones. It should be stressed, however, that cases in which deaths attributable exclusively to the effect of a toxic dose of a single cathinone remain rare.

The study of the fatal doses of these substances remains difficult as in most cases, synthetic cathinones are assumed with other drugs either voluntarily in order to reduce the side effects or to improve the desired ones, or because other drugs are already present in the purchased substance as adulterants. Moreover, there are also many cases of death classified by the authors as suicide in which subjects had previously made use of synthetic cathinones, not being clear if subjects consumed synthetic cathinones with the aim of committing suicide or if they were driven to commit suicide by the use of the substance.

The present review examined fatal cases in which synthetic cathinones were detected with the purpose of indicating what concentrations in the blood of these substances can with certainty be considered fatal.

In 2018, Zaami et al. conducted a previous descriptive review that included 20 articles dealing with mephedrone, MDPV, methyline, ethylone, butylone relating deaths concluding that only rarely the concentration of these substances in fatal cases exceeded 1000 ng/mL\(^5\).

In our study we enlarged the time window of analysis including a greater number of substances, noting that in most cases, deaths were attributed to multi-drug intoxication. In these fatal cases, synthetic cathinone concentrations were very different, suggesting the synergistic role that the other substances play in the determinism of death.

In very few cases, death could be ascribed exclusively to the use of synthetic cathinones, namely mephedrone, butylone, methyline, α-PVP, 3,4-DMMC, MDPBP, N-PP, 4-MEC.

In fact, at present, the literature reports 3 cases in which death was surely caused by mephedrone intoxication with haematic concentrations ranging from 980 ng/mL to 5500 ng/mL. Only 4 cases have been described as due exclusively to fatal methyline intoxication with blood concentrations ranging from 670 ng/mL to 840 ng/mL. In cases of α-PVP-intoxication in post-mortem blood, concentrations ranged from 174 ng/mL to
>20,000 ng/mL. In two, 3,4-DMMC overdose intoxications the fatal concentrations of the drug varied from 3310 ng/mL to 27,000 ng/mL. There is only a single case of death caused by 4-MEC fatal intoxication with haematic concentration reported of 14,600 ng/mL. A case of fatal N-PP\textsuperscript{89} intoxication showed a concentration of this substance in the blood of 3.200 ± 0.68 µg/mL intraday 3.1 ± 0.23 µg/mL interday. The toxicological analyses revealed the presence of MDPBP in a case of overdose with a blood concentration of 9.32 µg/cm\textsuperscript{385}.

In general blood concentrations that resulted in overdose for these substances were generally higher than 500 ng/mL (76.47% of overdose caused by a single synthetic cathinone), and in half cases, the concentration of the drug went beyond the value of 1 mg/L in blood.

However, it must be considered that our analysis was carried out on a very limited number of cases and that data available are scarce to draw definitive conclusions about the toxicity profile of these substances. In addition, as suggested by Kraemer\textsuperscript{106} interpreting post-mortem, drug levels require consideration of several possibilities influencing or altering corresponding concentrations. Measured post-mortem concentrations do not necessarily represent concentrations present at the time of death, due to post-mortal redistribution or possible degradation of the substance. Moreover, for synthetic cathinones volume of distribution is sometimes not known and information about drug distribution in tissues must be compared with individual case data. For these reasons, information about circumstantial data and information on age, state of health, drug-taking history, hair analysis can be helpful in interpreting toxicological data.

**Autopsy findings in cases of overdose from synthetic cathinones**

The review also focused on the examination of the autopsy findings in cases of death attributed exclusively to the use of synthetic cathinones. Pathological findings recorded in cases of death cases attributed exclusively to the use of methylene, appear to correlate with the hyperactivation of the sympathetic system with cardiac failure, malignant hyperthermia and rhabdomyolysis\textsuperscript{107–110}. In most cases, autopsy did not detect significant alterations. Catecholamines cardiac toxicity is well documented resulting in acute contraction band lesions attributed to relative hypoxia, increased sarcolemmal permeability, calcium overload, elevation of cAMP, activation of α- and β-ARs, and formation of oxidative catecholamine metabolites\textsuperscript{111}. Chronic catecholamine administration in rats causes interstitial fibrosis, promotes cardiac apoptosis, and induces contractile dysfunction primarily through left ventricular dilatation\textsuperscript{112}. In addition, alterations in the 5-HT system have been found to be associated with malignant hyperthermia\textsuperscript{113,114}.

Pearson\textsuperscript{61} described three cases of deaths resulting from malignant hyperthermia determined by methylene ingestion, that was found in blood in concentration of 840, 3300 and 560 ng/mL, concluding that peripheral blood methylene concentrations in excess of 500 ng/mL may result in death due to its toxic properties. In 2017 Deroux\textsuperscript{86} described another case of fatal intoxication due to the consumption in methylene of a 20-year-old male who, after attending a rave party, developed malignant hyperthermia, metabolic acidosis and rhabdomyolysis.

Also, in cases of death related to mephedrone and α-PVP autopsy data are indicative of acute cardiac pump failure from hyperactivation of the sympathetic system.
In 2011, Maskell\textsuperscript{58} described a case of mephedrone overdose in a blood concentration of 980 ng/mL in a 49-year-old female who insufflated approximately 0.5 g of mephedrone. Before taking the mephedrone, she consumed alcohol and smoked cannabis which were not found in her blood. Autopsy revealed an old atherosclerotic occlusion of the proximal anterior descending coronary artery and a 15-mm diameter area of myocardial fibrosis within the anterior left ventricular wall near the apex. Histopathological examination disclosed additional diffuse fibrosis of the left ventricular myocardium, but no evidence of acute ischaemia. Death was attributed to the adverse effects of mephedrone with atherosclerotic coronary artery disease and myocardial fibrosis being contributing factors. Adamowicz\textsuperscript{63}, in the same year, reported a case of fatal intoxication in a 30-year-old man, found in a critical condition on staircase. An autopsy showed brain stem failure and lung injury. The histopathological examination was negative. Mephedrone was found in his blood and vitreous humour at the concentrations of 5500 and 7100 ng/mL, respectively, revealing that this was fatal mephedrone intoxication.

In 2013, Saito\textsuperscript{67} reported the case of a 32-year-old man who died from a fatal intoxication with α-PVP, found with a blood concentration of 486 ng/mL. Autopsy findings were unremarkable. In 2014, Nagai\textsuperscript{102} described the case of a 25-year-old male who suddenly died after an episode of extreme violence against his roommates. Histology indicated diffuse and severe myocardial contraction bands, reflecting sympathetic nerve-mediated hypercontraction, as well as unusual lipid infiltration and disarray in the left ventricle. Post-mortem blood showed an α-PVP concentration of 411 ng/mL. In 2016, Potocka-Banà\textsuperscript{83} reported another case of a young man who was hospitalized due to sudden cardiac arrest. Macroscopic inspection revealed characteristics of generalized congestion of internal organs, including cerebral and pulmonary oedema, without signs of post-traumatic lesions or changes indicative of chronic disease. Histopathological examination of organ samples taken post-mortem (HE staining) showed oedema in the brain, oedema in the lung, acute congestion, alveolar haemorrhaging signs of chronic haemostasis and cardiac fibrous tissue replacement. Toxicological analysis of the samples revealed the presence of α-PVP in blood with a concentration of 174 ng/mL. Based on these results, cardiac arrest resulting from α-PVP intoxication was considered the direct cause of death. Also, in 2016, Wright\textsuperscript{95} described two cases of α-PVP overdose. The two men of 37 and 34 years old showed an α-PVP concentration in blood of 54 ng/mL and <20,000 ng/mL, respectively, no information about pathological aspects was available.

In the literature, two 3,4-DMMC one 4-MEC overdose intoxications have been reported. Also in these cases, lesions capable of explaining death were not identified at autopsy.\textsuperscript{76,99,103} In 2012, Rojek et al.\textsuperscript{49} described a case of suicide where a 21-year-old ingested 10 tablets of dibutydrone and died after repeated cardiac arrests. In this case, there was also information about the hospitalization. After admission, he developed seizures, symptoms of haemorrhagic diathesis manifested as skin petechiae, bleeding from the gastrointestinal and respiratory tract, as well as bleeding from puncture sites. Finally, he developed cardiac arrest with asystole.

In 2018, Majchrzak\textsuperscript{89} described a case of fatal N-PP intoxication for the first time. Autopsy revealed cerebral oedema, pulmonary oedema and passive congestion of internal organs, and it was concluded that acute respiratory distress was the direct cause of death.
The strength of our study is represented by the number of articles included in the review. The limits are represented by the choice of analysing a small number of cathinones of the limited amount of data available and by the necessary reference to articles written by other authors.

**Conclusion**

At present, pointing out fatal overdose concentrations has been possible only for few synthetic cathinones and more data are necessary in order to better understand their toxicity and relative fatal concentrations for man.

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**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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