

# Synthetic cathinones related fatalities: an update

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**Abstract. – OBJECTIVE:** Synthetic cathinones, more commonly known as “bath salts”, are synthetic drugs chemically related to cathinone, a psychostimulant found in the khat plant. They are the first most consumed products among new psychoactive substances, which cause psychostimulant and hallucinogenic effects determining a number of fatalities worldwide. In this paper, we have systematically reviewed cases of synthetic cathinones-related fatalities analytically confirmed, which have occurred in the last few years.

**MATERIALS AND METHODS:** Relevant scientific articles were identified in Medline, Cochrane Central, Scopus, Web of Science and Institutional/government websites up to November 2017 using the following keywords: synthetic cathinones, mephedrone, methylenedioxypyrovalerone, MDPV, methylone, ethylone, buthylone, fatal intoxication, fatalities and death.

**RESULTS:** In total, 20 citations met the criteria for inclusion, representing several fatal cases with analytically confirmed synthetic cathinones in biological sample/s of the deceased. The death was attributed to hyperthermia, hypertension, cardiac arrest and more in general to the classic serotonin syndrome. Only rarely did the concentration of the parent drug causing fatality overcome the value of 1 mg/L in *post-mortem* biological fluids.

**CONCLUSIONS:** Abuse of synthetic cathinones still represents a serious public health issue. Systematic clinical studies on both the animal and human model are lacking; therefore, the only available data are from the users who experience the possible hazardous consequences. Analytical methodologies for the identification of parent compounds and eventual metabolites both in *ante-mortem* and *post-mortem* cases need to be developed and validated. Analytical data should be shared through different communication platforms with the aim of stopping this serious health threat for drug users.

*Key Words:*

Synthetic cathinones, Fatalities, Serotonin syndrome, Bath salts.

## Introduction

Synthetic cathinones, more commonly known as “bath salts”, are synthetic drugs chemically related to cathinone, a psychostimulant found in the khat plant. They are the first most consumed products among new psychoactive substances exerting psychostimulant and hallucinogenic effects, similar to those of cocaine, 3,4-methylenedioxymethamphetamine (MDMA), amphetamines and methamphetamines<sup>1,2</sup>. Indeed, they are marketed as cheap substitutes for the latter compounds. Synthetic variants of cathinone can be much more potent than the natural product and, in some cases, very dangerous or even lethal<sup>3</sup>. A number of synthetic cathinones related deaths have been published<sup>1</sup>. Synthetic cathinones, referred to as “bath salts”<sup>4</sup>, can be found in the form of a brown or white crystal-like powder and are sold in small foil or plastic packages labeled as “not for human consumption”, “jewelry cleaner”, “plant food” or “phone screen cleaner”. They are available online and in drug paraphernalia stores under a variety of brand names, such as Flakka, Cloud Nine, Lunar Wave, White Lightning, Bloom, Scarface and Vanilla Sky. In 2013, European countries reported more than 110 NPS products containing a combination of up to seven different NPS compounds sold as one product. Synthetic cannabinoids were found to be present in more than 55% of these NPS

products, and synthetic cathinones were present in more than 25%<sup>5</sup>.

In some countries, shortage of heroin and an increase in local availability of synthetic cathinones contributed to high-risk drug users switching to injecting NPS, primarily synthetic cathinones, as reported by WDR 2016. New synthetic cathinones are continuously emerging; although data collection for 2015 is still in progress, 75 new substances have been reported to UNODC for the first time, among which 20 belong to synthetic cathinones group compared to 21 newly emerged synthetic cannabinoids. Moreover, global seizures of synthetic cathinones have been steadily increasing since they were first reported in 2010. Those seizures tripled between 2013 and 2014, reaching 1.3 tons. Most synthetic cathinones were seized in Europe and in East and South-East Asia<sup>5</sup>. The acute and chronic toxicity of many synthetic cathinones is unknown or very sparsely investigated. Information of related fatalities has not been recently systematized. In this review, we aimed to report most recent analytically confirmed cases of synthetic cathinones-related fatalities.

## Materials and Methods

Relevant scientific publications were identified from Pubmed, Cochrane Central, Scopus, Web of Science and Institutional/government websites up to November 2017 using the following keywords: synthetic cathinones, mephedrone, methylenedioxypyrovalerone, MDPV, methylone, ethylone, buthylone, fatal intoxication, fatalities and death. The first seven keywords were individually searched and then in association to each of the last three. Inclusion criteria were as follows: 1) articles had to be written in English; 2) described human administration of one or more synthetic cathinones was required; 3) analytically confirmed the presence of one or more synthetic cathinones was required; 4) death had to be attributed to one or more synthetic cathinones either alone or in combination with other substances.

## Results

After an initial screening, a total of 96 citations were identified, but only 20 met the inclusion criteria. Ten different compounds were found as the cause of synthetic cathinones fatalities and their structural formula has been reported in Figure 1.

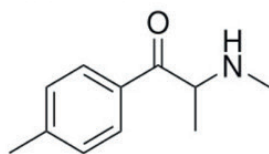
It has to be noted that in some cases the ingestion of a synthetic cathinone was not the direct cause of death, but any event related to a psychotropic effect of the drug should be in any case taken into account. In briefly, in some below-described cases, drug users died for different causes, the most frequent of them being suicides. Nevertheless, it can be hypothesized that on the one hand users could have consumed synthetic cathinones with the aim of committing suicides; on the other hand users committed suicides under the psychoactive effects of the drug(s).

Fatalities associated with the most renowned cathinone, mephedrone, have been recently reviewed by Busardò et al<sup>1</sup> in 2015. Only 18 fatal cases were listed with analytically confirmed drug in *post-mortem* biological sample/s. The death was attributed to exclusive mephedrone intoxication in 9 cases (range of *post-mortem* blood mephedrone concentration: 1.33-22 mg/L), whereas mephedrone together with other drugs of abuse was reported as cause of death in 6 cases (range of *post-mortem* blood mephedrone concentration: 0.04-1.3 mg/L). Similarly, in the same years covered by the above-reported review, analysis of information come from the United Kingdom National Programme on Substance Abuse Deaths disclosed 128 alleged mephedrone-associated fatalities<sup>6</sup>. However, only in 36 cases, mephedrone was identified in *post-mortem* biological samples and only in 10 cases mephedrone was identified as the only drug of abuse with mean concentrations of 1.43 mg/L (range = 0.03 – 22.0 mg/L) when it was presented with other drugs. A mean value of 1.996 mg/L (range = <0.01 – 12.15 mg/L) when it was the sole drug. These figures excluded one combined mephedrone case with a level of > 2000 mg/L. Death occurred mainly in weekends and typical victims were white males, with a previous history of drug abuse.

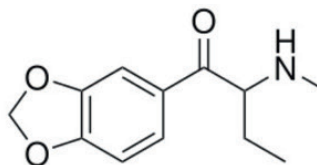
In a description of a synthetic cathinones, related fatalities occurred in Miami (USA); in 2013 methylenedioxypyrovalerone (MDPV) intoxication has been reported as a cause of death in a 15 out of 23 cases. In 2 out of 4 hanging suicides, MDPV was the only significant drug found at a concentration of 0.10 and 0.64 mg/L peripheral blood. In all the other cases the presence of other psychoactive substances, mainly benzodiazepines, opioids and antidepressant drugs, was disclosed with an average of 0.109 mg MDPV per L peripheral blood<sup>7</sup>.

In addition to this case series study, some MDPV-related fatalities have been described, all

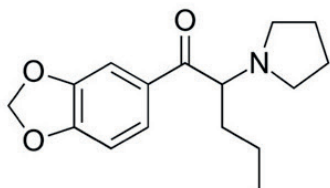
**Mephedrone (4-methyl-N-methylcathinone)**



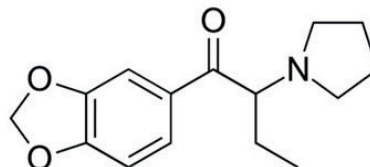
**Butylone ( $\beta$ -keto-N-methylbenzodioxolylbutanamine,  $\beta$ k-MBDB)**



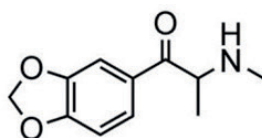
**Methylenedioxypropylvalerone  
(3,4-Methylenedioxypropylvalerone, MDPV)**



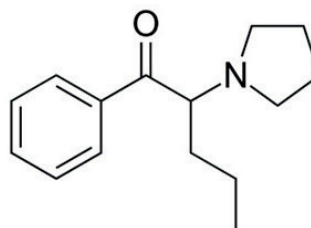
**3',4'-Methylenedioxy- $\alpha$ -pyrrolidinobutyrophenone (MDPBP)**



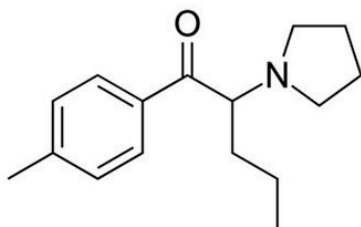
**Methylone  
(3,4-Methylenedioxy-N-methylcathinone, MDMC,  $\beta$ k-MDMA)**



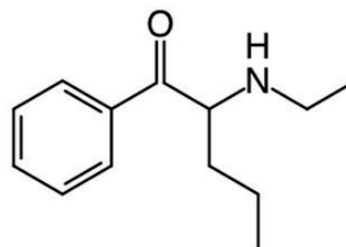
**Alphapyrrolidinovalerophenone ( $\alpha$ -Pyrrolidinopentiophenone,  $\alpha$ PVP)**



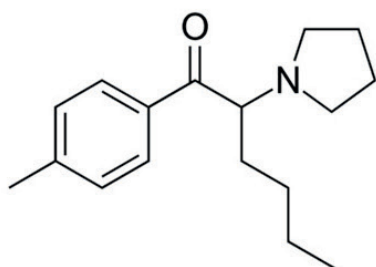
**Pyrovalerone (4'-Methyl-2-(1-pyrrolidinyl)valerophenone)**



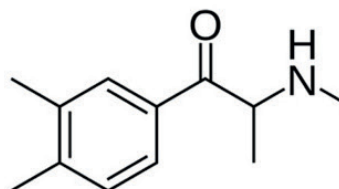
**$\alpha$ -ethylaminopentiophenone ( $\alpha$ -EAPP)**



**4'-Methyl- $\alpha$ -pyrrolidinohexiophenone (MPHP)**



**3,4-dimethylmethcathinone (3,4-DMMC)**



**Figure 1.** Molecular structures of synthetic cathinones involved in drug-related fatalities

with the common characteristics of hyperthermia and hypertension.

Firstly, in 2011 a raving man presented at the Emergency Room in a Baltimore hospital (MD,

USA), in a delirium state. Once there, he developed ventricular tachycardia, hyperthermia, and died. Comprehensive drug testing showed heart blood with 0.7 mg/L MDPV and peripheral blood with 1.0 mg/L MDPV. The cause of death was declared as MDPV fatal intoxication<sup>8</sup>.

Subsequently in 2012, in North Carolina (USA), a 40-year-old male who injected and snorted “bath salts” containing MDPV, became aggressive, uncontrollable and was admitted to the Emergency Department for bradycardia and subsequent cardiac arrest with MDPV present in his urine (0.670 mg/L) and serum (0.082 mg/L) analyzed at the time of admission. Later on, he developed hyperthermia, rhabdomyolysis, coagulopathy, anemia, thrombocytopenia, acidosis, anoxic brain injury and finally died<sup>9</sup>. The same symptoms were explained in 2013 in USA for a 20-year-old male and a 48-year-old female, both of whom presenting in addition a disseminated intravascular coagulation. The cathinone could be only detected in the *ante-mortem* blood of the male and measured in *post-mortem* blood of the female at a concentration of 29 mg/L<sup>10</sup>.

This latter extremely high MDPV concentration found in *post-mortem* blood represented an isolated case. Indeed, in all the others, the drug was lower than 1 mg per L biological fluid. This evidence, already enlightened in the previous cases, was also confirmed in a death occurred in 2013 (Cleveland, OH, USA). A 39-year-old male died for a cardiac arrhythmia following the ingestion of MDPV. The drug was uniformly distributed among multiple tissues (blood, brain, muscle, cerebrospinal fluid and lung) at concentrations of approximately 0.4 to 0.6 mg/L. A femoral blood concentration 0.44 mg/L was judged sufficient to cause death<sup>11</sup>.

As in the previous case of a firstly observed fatality due to MDPV, a primarily case series of deaths due to methylone were reported in Baltimore (MD, USA) in 2012. Four *post-mortem* cases with suspicion of bath salts consumption were analyzed for cathinones, with drug levels quantitated in multiple biological matrices. All four cases showed detectable concentration of methylone, with heart blood concentrations of 0.740, 0.118, 0.060 and 1.12 mg/L. Also, two cases had MDPV presented. In all cases, the cause of death was defined as “accidental”<sup>12</sup>.

Drowning due to acute methylone intoxication was diagnosed in a healthy 19-year-old woman with a history of recreational drug use found in 2013 floating face down near the shore of a po-

pular beach in San Diego, (CA, USA). Methylone was detected as sole psychotropic drug in the peripheral blood, central blood, vitreous, liver and gastric contents of 3.4 mg/L, 3.4 mg/L, 4.3 mg/L, 11 mg/kg, and 1.7 mg, respectively<sup>13</sup>.

In the same 2013, once again in San Diego, a case of sudden death related to methylone (3,4-methylenedioxy-N-methylcathinonmethylone) was evidenced in a healthy 19-year-old man, who consumed the drug, collapsed while jogging and died. Autopsy showed pulmonary congestion and edema, mild peribronchial inflammation, and mild hepatic portal and lobular inflammation.

Although the few reported fatalities due to methylone prevented a comparison of blood methylone concentrations between this case and existing reports, the amount of *post-mortem* blood methylone (0.07 mg/dL or 0.7 mg/L) appeared to be below those reported in other drug-related fatalities<sup>14</sup>.

The fact that lethal concentrations of cathinones cannot be yet established, being available data very scarce, has been confirmed by two cases of cathinone-related deaths occurred in New York City area (NJ, USA). Indeed, conducting a 3-year retrospective analysis of deaths in which cathinones were detected, two groups came out: 15 cases in which cathinones were a contributory cause of death together with many other ingested drugs of abuse and other 15 cases in which they were an incidental finding, but death causes were suicides, accidents, etc. In this case series, there were only two deaths attributed to acute cathinones intoxication, both with few hours’ survival after cathinone ingestion. One was a 20-year-old man who presented to the Emergency Department unresponsive and with a body temperature of 41.6°C, after having consumed the drug at a rave party. He survived for 10 h. His *post-mortem* heart blood methylone concentration was 0.71 mg/L. The other was a 25-year-old woman found unresponsive in bed after a night party. At hospital she was resuscitated and survived 10 h more. Her *post-mortem* femoral blood ethylone concentration was 1.7 mg/L. In both case, cathinones concentration in *post-mortem* blood was not significantly higher than those in the other presented cases<sup>15</sup>.

This case of ethylone fatality was not the only one. In 2015, nine *post-mortem* cases in whom ethylone was identified in blood, were evidenced in Gainesville, (FL, USA). In seven of the cases ethylone could be measured in blood, at a concentration from 0.038 to 2.572 mg/L; in one case ethylone was detected but not quantified and one case did not have detectable ethylone in blood.

Besides ethylone, eight cases were also positive for 11-nor-9-carboxy- $\Delta^9$ -tetrahydrocannabinol and seven cases to other drugs of abuse<sup>16</sup>.

In contrast with previous statement on the impossibility to establish fatal cathinones concentrations, the County Medical Examiners of Tampa (FL, USA) in 2012 affirmed that peripheral blood methylone concentrations more than 0.5 mg/L may result in death due to its toxic properties, being the main elevated body temperature and other sympathomimetic-like symptoms. This was the deduction coming from three fatal intoxications cases following methylone consumption. In all three fatalities, the deceased exhibited seizure-like activity and body temperatures higher than 40°C before death. Peripheral blood methylone concentrations in the three fatal cases were 0.84, 3.3 and 0.56 mg/L<sup>17</sup>.

A case of a death following consumption of methylone in a party was also reported in France (Europe) in 2016. High concentrations of methylone were found in the peripheral blood (3.13 mg/L) and in the central blood 6.64 mg/L of a 21-year-old man deceased for a respiratory distress. Drug presence in the gastric contents provided evidence that the substance was taken orally. The analysis of the peripheral blood and the urine showed an absence of any other drug of abuse or medication. The product seized by the investigators was a shiny, white, fine-grained powder containing methylone, with a degree of purity of 83.3%<sup>18</sup>.

A severe hyperthermia (41.2°C) with hypertension, increased muscle tonus and sialorrhea was noted in a 21 years old male admitted at Intensive Care of the Hospital in Nowy Targ (Poland) in 2012 following the suicidal ingestion of 10 tablets of an internet-sold bath salt: “Amph-i-bia”. The man died after repeated cardiac arrests with asystole. Butylone (bk-MBDB) was identified and quantified at concentrations of 20 mg/L in the blood and 33 mg/kg in the liver samples for the deceased. This case report was a further confirmation of the serotonin toxidrome triggered by a synthetic cathinone<sup>19</sup>.

A capsule containing both 422 mg methylone and 53 mg butylone was the cause of multi-system organ failure and consequent death in a healthy 24-year-old girl who ingested the capsule sold as “ecstasy” at a concert. The patient presented to the Emergency Department with a classical serotonin syndrome (comatose febrile, tachycardic, tachypnic, and hypertensive status). Laboratory analysis identified only methylone and butylone in girl urine, but did not quantify them<sup>20</sup>.

Fatalities following the ingestion of synthetic cathinones occurred also in Japan, as shown in

a retrospective study of forensic autopsies, at the Department of Legal Medicine of Tokyo Women’s Medical University between January 2011 and January 2015. Among 359 autopsies, in only 3 cases, different synthetic cathinones were found as the cause of death and they were detected (even if concentration values were not reported) in *post-mortem* fluids. One fatal intoxication was due to 3',4'-Methylenedioxy- $\alpha$ -pyrrolidinobutyrophenone (MDPBP), one to simultaneous ingestion of methylenedioxy-pyrovalerone (MDPV), alphapyrrolidinovalerophenone ( $\alpha$ -PVP), pyrovalerone and finally one due to 4'-methyl- $\alpha$ -pyrrolidinohexiophenone (MPHP)<sup>21</sup>.

Apart from the above reported fatalities due to synthetic cathinones, most sold in the web sites and well known among users, there have been also some isolated fatalities due to less frequently used products.

In a Japanese study, which reviewed from 2012 to 2014 poisonings due to synthetic cathinones and cannabinoids in six patients aged 22-42 years old, only one fatal case was pointed out, in which, a consumer of synthetic cannabinoids and cathinones experienced cardiopulmonary arrest, acute circulatory failure and death after consumption of mepirapim (a synthetic cannabinoid) and  $\alpha$ -ethylaminopentiophenone ( $\alpha$ -EAPP). Concentration of  $\alpha$ -EAPP found in serum was 3.1 mg/L<sup>22</sup>.

1-phenyl-2-(1-pyrrolidinyl)-1-pentanone ( $\alpha$ -PVP) caused cardiac arrest in a young man, admitted to the Intensive Care Unit of the Szczecin Hospital (Poland) in 2016. Laboratory analyses revealed the presence of  $\alpha$ -PVP in the following concentrations: blood 174 ng/mL, urine 401 ng/mL, brain 292 ng/g, liver 190 ng/g, kidney 122 ng/g, gastric contents 606 ng/g<sup>23</sup>.

Finally, 3,4-dimethylmethcathinone (3,4-DMMC) was found in external iliac vein blood and urine at concentration of 27 mg/L and 7.6 mg/L, respectively from a heroin user found dead by his parents in his apartment with a *post-mortem* interval estimated to be approximately 1.5 days. Plastic packets of a product labeled as “LOOP 3” were found in the bedroom. These packets contained a fine white powder identified by forensic analyses as 3,4-DMMC, the synthetic cathinone found in *post-mortem* fluid of the deceased<sup>24</sup>.

## Discussion

Although the presented results showed some case series of synthetic cathinones related fatalities, the evidence on deaths caused by these

substances is still scarce and spreads in different parts of the world. It should be emphasized that the disclosure of synthetic cathinones-related fatalities real figures can be hindered by several factors, including lack of specific analytical methods for biological samples, and consumed product testing, polydrug use. In this latter concern, these products sold as “bath salt” or “plant feeders”, etc. could also contain other NPD, such as synthetic cannabinoids or piperazines. Indeed, in most intoxication cases where biological samples have been analyzed other psychoactive substances and/or their metabolites have been detected. It is likely that some of these substances are consumed to counteract the unwanted effects of cathinones, for example benzodiazepines to reduce anxiety, panic attacks, or insomnia. Conversely, others can result in synergic effects such as cocaine, amphetamine-type substances or selective serotonin reuptake inhibitors antidepressants with a possible increased sympathomimetic toxicity up to serotonin toxidrome. Finally, natural but most importantly synthetic cannabinoids can increase hallucinations<sup>25</sup>.

The new psychoactive substances market alongside the “legal highs” or bath salts, which are the most sold and consumed, has reached new groups of consumers with the alleged promises of new and prolonged sensations<sup>26</sup>. Among them, also the hypothesized possibility to facilitate and/or to enhance sexual intercourses when using psychostimulant drugs, including synthetic cathinones mostly among men who have sex with other men in a context recently defined as “chemsex”<sup>27</sup>.

The reality is that both effective and toxic doses of these substances are unknowns; systematic clinical studies on both animal and human model are lacking and users are the sole experimenters with possible hazardous consequences<sup>28</sup>.

## Conclusions

In reviewing and showing data regarding synthetic cathinones related fatalities, we wish to draw the attention of the whole scientific community on the importance of improving surveillance and data sharing through national and international early warning systems and a standardization in reporting related deaths. Analytical methodologies for the identification of parent compounds and eventual metabolites both in *ante-mortem* and *post-mortem* cases should be developed, valida-

ted, and analytical data shared through different communication platforms with the aim to contain this serious threat for the health of drug users.

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## Conflict of Interest

The Authors declare that they have no conflict of interest.

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