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The novel psychoactive substance 3-methylethcathinone (3-MMC or metaphedrone): a review

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Highlights

- 3-MMC-related morbidity and mortality has alarmingly increased in recent years
- Most 3-MMC consumption concerns polydrug abuse
- 3-MMC is a substrate-type monoamine releaser
- Tachycardia and agitation are the clinical symptoms most frequently reported
- Concentrations of 3-MMC reported in fatal and non-fatal intoxications overlap

Abstract

3-Methylethcathinone (3-MMC or metaphedrone) is a synthetic cathinone, recently introduced in the market of the new psychoactive substances (NPS), initially to
replace mephedrone (4-methylmethcathinone or 4-MMC), and rapidly widespread among drug users. 3-Methylmethcathinone is legally controlled in many countries, but is still easily available for purchase from websites, and frequently found in recreational settings. Most toxicological data on this drug come from human case reports following intoxications. Thus, further investigation on their pharmacological and toxicological properties is necessary to evaluate its potential harmful effects. The present work provides a review on the available data about 3-MMC legal status, chemistry, patterns of use, prevalence, biological effects, toxicokinetics, toxicity and factors affecting stimulant/toxicological effects.

Keywords

1. Introduction
Cathinone derivatives are synthetic ring-substituted phenylethylamines, analogues of cathinone, a natural psychoactive substance found in the leaves of the Catha edulis plant, known as khat. The first synthetic cathinones were synthetized in the late 1920’s for medical purposes and began being sold as recreational drugs in the 2000’s [1]. Methcathinone (ephedrine) and 4-methylmethcathinone (4-MMC or mephedrone) were the first synthetic cathinones [2]. These drugs are often sold as “bath salts” or “plant food” [2] and labelled “not for human consumption” or “research chemical” to circumvent drug abuse laws [3]. These and other frequently abused synthetic cathinones are shown in Fig. 1.

4-Methylmethcathinone is one of the most popular synthetic cathinones, and its abuse was first detected in 2007 [4]. Users of 4-MMC describe its effects as similar to those of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) but with stronger feelings of craving [5]. The most frequently used routes of administration are insufflation (snorting) and per os, either through the ingestion of capsules or powder wrapped in cigarette paper (referred to as “bombing”) [5]. Inhalation and intravenous injection are also used, but more rarely [8]. As its consumption increased, toxicity reports also peaked and, as a result, several countries banned 4-MMC. In consequence, the market quickly evolved for a new generation of synthetic cathinones, with the
appearance of new structurally-related derivatives [6]. In this context, 3-methylmethylcathinone (3-MMC or metaphedrone) first appeared in Sweden in 2012 as a “legal drug” to replace 4-MMC [7], and was mostly sold on the internet as a “research chemical”. Like other synthetic cathinones, 3-MMC has no known therapeutic use [8].

This novel designer drug is usually found in the form of white powder or crystals (Fig. 2). Users describe its effects as similar to, but less potent and intense than those of MDMA and 4-MMC [9]. Repeated administration in a single session is a common consequence of the short duration of its desired effects and this may be attributed to the short half-life of 3-MMC [6].

Presently, 3-MMC is a controlled substance in several European countries, such as Sweden, France, Germany, Czech Republic, Poland and UK [6, 7, 9, 10]. In Portugal, the list of controlled substances was updated in 2012 (Law 13/2012, 26th March), which included thereafter 4-MMC, 3-MMC and isomers. The drug is also controlled in some countries outside Europe, namely Israel and USA [6].

Most toxicological data on this drug come from human case reports following intoxications. Thus, further investigation on their pharmacological and toxicological properties is necessary to evaluate its potential harmful effects. The present work provides a review on the available data about 3-MMC legal status, chemistry, patterns of use, prevalence, biological effects, pharmacokinetics, toxicity and factors affecting stimulant/toxicological effects.

2. Methods

An exhaustive literature search was carried out in PubMed (U.S. National Library of Medicine), without a limiting period, to identify relevant articles. “3-Methylmethylcathinone”, “3-MMC”, and “synthetic cathinones” were used as search keywords. Furthermore, the retrieved journal articles as well as governmental, European committees, and United Nations documents, including reports from The United Nations Office on Drugs and Crime (UNODC, https://www.unodc.org), European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, http://www.emcdda.europa.eu) and World Health Organization (WHO, http://www.who.int), were further reviewed to find additional data related to the drug.
3. Physicochemical properties and analytical methods for identification
Chemically, synthetic cathinones are analogues of the natural cathinone, which in turn is closely related to amphetamines, with the addition of a ketone group at the β-position of the amino alkyl chain, which is attached to the phenyl ring [2]. 3-Methylmethcathinone, also known as 2-(methylamino)-1-(3-methylphenyl)propan-1-one, is a ring substituted cathinone with a methyl group attached to the third carbon atom of the phenyl ring [11]. Two enantiomers of 3-MMC exist, R-3-MMC and S-3-MMC, due to the chiral centre at the C-2 carbon (β-position) of the propane side chain (Fig. 1) [8]. Similarly to cathinone, it is expected that the S form of 3-MMC is more potent than the R form [8] but this hypothesis requires confirmation.

As depicted in Fig. 3, 3-MMC is available as a free base or as a hydrochloride salt that can be synthesized through the reaction of 3-methylbenzaldehyde (1) with ethyl magnesium bromide, followed by oxidation with pyridinium chlorochromate on silica gel, and bromination with hydrobromic acid and hydrogen peroxide to obtain the bromo ketone (4). Then, the reaction with ethanolic methylamine will produce the 3-MMC free base (5). The free base can be converted into 3-MMC hydrochloride salt (6) by adding ethereal hydrogen chloride. The purity of 3-MMC can vary according to the purification steps performed during its synthesis [12]. Additional chemical properties of 3-MMC are presented in Table 1.

A number of analytical methods have been developed for the identification of cathinones, both in seized materials and in biological fluids of intoxicated individuals. In 2011, Power et al. synthesized and analysed 3-MMC through gas chromatography–mass spectrometry (GC-MS), infrared (IR) and nuclear magnetic resonance (NMR) [12]. In 2013, Christie et al. [13] demonstrated that Raman spectrometry can distinguish regioisomers of cathinones, including 3-MMC, and this method is specially advantageous when a fast and reliable identification is needed, as for example at airport security settings. Another great advantage of this method is the portability of the Raman microscope. In 2014, Strano Rossi et al. [14] described analytical approaches to identify different types of new psychoactive substances (NPS) in seized materials using GC-MS, liquid chromatography–high resolution mass spectrometry (LC-HRMS), and NMR. Currently, the most frequently used method for the identification of 3-MMC is liquid chromatography with different detectors, such as liquid chromatography tandem-mass spectrometry (LC-MS/MS) [6, 7, 9, 11, 15]
and LC-HRMS [16]. The second most frequently used method is GC-MS [10, 11, 15, 17-19]. Regarding the GC-MS methodology, Zuba and Adamowicz [11] suggest that it is better fitted for analysis of seized drugs. As the GC-MS method is less sensitive than the LC-MS/MS method, the latter is more suitable for toxicological analysis of biological specimens [11]. The LC-HRMS method is one of the most specific and sensitive methods for hair sample analysis, while the NMR method is mostly used when there is a need to distinguish between isomers [14, 19] but can also be applied for determining purity. The identification of substances is crucial in forensics and for such purpose the combination of different analytical methods seems to provide a more reliable identification of the substance [11].

4. Appearance, patterns of consumption, and prevalence

Like most “legal highs”, 3-MMC is usually sold online in the form of off-white crystals or white powder with a lycorine-like smell [10], often labelled as “research chemical” and/or “not for human consumption” [18]. The price ranges from 11 € to 35 € per gram [20, 21]. Similarly to 4-MMC, consumption mostly occurs through insufflation (snorting) and oral ingestion [6, 7, 9, 10, 22], but the intravenous injection of the drug has also been reported [7, 9, 10].

In Germany, Marillier et al. [23] analysed the purity of product samples donated by identified NPS users. From the 31 samples collected, 8 were positively confirmed for the presence of 3-MMC, although only 7 users admitted to be aware that the drug bought was 3-MMC. Those 8 samples had a range of purity between 51 % and 88 %. Reports from users of 3-MMC indicate drug administration doses often ranging from 50–250 mg, but larger amounts were occasionally described (up to 500 mg), with repeated administrations to prolong the desired effects adding up to ingestions that could reach 2 g in a single session [9]. This scenario is similar to that of 4-MMC, in which case, for the same reason, the users take between 150–250 mg in repeated administrations, resulting in ingestions of 0.5–1 g in a single session [6].

Studies conducted in Poland, Sweden, Hungary and Germany concluded that the users were mostly males with ages ranging from 17–50 years old [7, 9, 18, 24]. In Slovenia, other investigations found no gender differences in the drug consumption patterns and, although the age of the respondents included in the sample ranged from 15–40 (mean 23) years old, most of them were still attending school [22].
The prevalence of these drugs is difficult to measure because little data is available, and the existing information may not be accurate; questionnaires may not be reliable, as all too often consumers do not tell the truth about their consumption habits or do not know what they are buying. The same applies in case of intoxications without analytical confirmation. Some reported patterns of consumption are summarized in Table 2.

From 2012 to 2013, Institoris et al. [18] sampled suspected drug abusers in Hungary. Among 1959 individuals in Budapest and 472 individuals in South-East Hungary (Csongrád County) whose urines were confirmed positive for drug use, 3-MMC was detected in 0.97% and 5.07% of the cases, respectively [18]. In Germany, from 2010 to 2016, 81 intoxications with synthetic cathinones were reported by Romanek et al. [24]. From those, 13 tested positive for 3-MMC in only two years of the study, 8 in 2014 and 5 in 2015. The slight decrease observed in the detected number of cases might be a consequence of the implementation of the German narcotics law in December 2014 [25], although the small size of the sample precludes more robust conclusions.

In Poland, Maciów-Głąb et al. [26] tested 2075 samples of seized drug products from 2010 to 2015. The authors divided the samples into two categories, the first category consisting of powders, tablets and capsules, and the second category of dried plants. 3-Methylmethcathinone was found in products included in the first category, seized from 2013 to 2015. Before 2013, the cathinones reported in this category were butylone and MDPV (3,4-methylenedioxypyrovalerone), suggesting that 3-MMC was introduced to replace them. Also, the frequency of 3-MMC detection increased from 2013 to 2015, supporting the increased interest in the drug, as noted by Adamowicz et al. [27] for the same location and period (2013 and 2014).

An impressive report by Adamowicz et al. [27] presents the results of the drug-related cases analysed in the Institute of Forensic Research (Krakow, Poland) from 2012 to 2014. Succinctly, 3-MMC was detected in 50 of the 112 cases that were positive for NPS, being the most prevalent drug. Eleven cases occurred in 2013 and 39 cases in 2014, supporting the increasing interest in the drug [27]. The drug prevalence reported in this study is higher than that reported by Institoris et al. [18]. This could be explained by the small sample size in the Polish study, which may result in sample bias. Another explanation might be that the sample from Poland only includes NPS, while the sample from Hungary includes both classic drugs and NPS.
From May to October 2014, a questionnaire applied to 249 drug users in Slovenia revealed that 67.9% of the subjects had tried 3-MMC, while one-third of abusers admitted having used the drug in the past month [22]. As this questionnaire was performed online, it leaves out NPS consumers that do not have internet access.

The interest in a particular drug can also be measured in online forums. Ledberg [28] studied the interest in 8 NPS before and after scheduling. The author used the data extracted from the Flashback Forum, a Swedish Internet discussion forum, and measured the interest by counting the number of posts per day, 180 days before and after the respective drug being prohibited. For 3-MMC, the interest before scheduling hit a maximum around 80 posts per day (mean of 20 post per day) and around 5 posts per day after scheduling (mean of 3.1 posts per day) [28]. This is consistent with the pattern of analytically confirmed exposure to 3-MMC found in the Swedish STRIDA project (Swedish early warning system on NPS), that decreased when the substance was legally controlled [7]. Drug forums may also be important to obtain information on the substance dosing reported by users [28], which may be of great importance to adopt measures in case of intoxications or to plan a study on the toxicity of the selected drugs.

5. Biological effects

Most information on biological effects of 3-MMC in humans derives from case reports of intoxicated individuals that are admitted to the emergency room, from online questionnaires, and from self-reports of consumers of 3-MMC, but even these data are scarce.

The desired effects of 3-MMC are euphoria, excitement, high energy levels, stimulation (rushing), happiness, awareness of senses, and appreciation of music [9, 17]. As with amphetamines and other stimulant drugs of abuse, the social effects consist of improved social skills and feelings of empathy [9] but chronic abuse may trigger deterioration of relationships with family, partner and friends [22].

In what concerns the acute adverse effects of 3-MMC, verbosity, stuttering, fatigue, reduced level of consciousness, aggression, and uncoordinated movements were described, but tachycardia and agitation were the clinical symptoms most frequently reported [9]. Concentration difficulties, tingling in the arms and legs, hyponatremia, diaphoresis, seizures, hyperthermia, and rhabdomyolysis have been known to occur but with lower frequency [7, 22]. Other effects that have been reported include
hypertension, dilated pupils, hallucinations, fear, anxiety, depression, disorientation, slurred speech, strange behaviour, unsteady gait, and staggering, but these effects could not be unequivocally attributed to 3-MMC, as other substances were co-ingested [7, 9, 22]. Intoxication symptoms described in case reports from non-fatal intoxications are compiled in Table 3.

6. Pharmacological profile
Luethi et al [29] studied the potency of inhibition of the transporters of norepinephrine, dopamine and serotonin caused by 4-MMC analogues and the binding affinity to receptors and transporters of these monoamines. For 3-MMC, the authors found that the inhibition of the dopamine and norepinephrine transporters (DAT and NET, respectively) was significant and stronger than that for the serotonin transporter (SERT). This suggests that, similarly to 4-MMC, also 3-MMC exhibits amphetamine-like stimulant properties, as the drug is a substrate-type monoamine releaser and evokes release of norepinephrine and dopamine. The authors also found that 3-MMC strongly binds to serotonin 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} receptors and, in addition, has low micromolar affinity at α_{1A} and α_{2A} adrenergic receptors, which are known to play opposing roles in modulation of stimulant behaviour [30].

7. Toxicokinetics
Little data is available on the pharmacokinetics of 3-MMC. To the best of our knowledge no human studies are documented in the literature and only one study using animals is available [6]. Therefore, the pharmacokinetic features of 3-MMC are described below based on the work of Shimshoni et al. [6] in pigs. As this animal study is the only one so far reported, caution should be taken when interpreting the results due to the small sample size (n = 6) [6].

7.1 Absorption
In this study, the hydrochloride salt form of 3-MMC was administered orally or through intravenous injection. After a single oral dose of 3 mg/kg of the drug, the peak plasma concentration of 3-MMC (C_{max} = 27 µg/L) occurred at 5–10 min [6]. Only 7 % of the drug was orally absorbed. Absorption mostly occurred in the first 12 min (corresponding to more than 80 % of the absorbed drug). The low oral bioavailability may explain the preferred use of 3-MMC through insufflation [6].
Among the hypothesises to explain poor absorption of 3-MMC are the extrusion of the drug by efflux pump in the gut or its first-pass metabolism before reaching systemic circulation [6]. After a single intravenous dose of 0.3 mg/kg of 3-MMC, almost none of the drug was detected in plasma after 4 h (detection limit of the method was 0.1 µg/L) [6]. Due to similar pharmacokinetic characteristics, the need for binging and mixing routes of administration to achieve both rapid and long-lasting effects were also previously noted for other synthetic cathinones [2].

### 7.2 Distribution

3-Methylmethcathinone had a total clearance of 199 L/h and a volume of distribution of 240 L [6]. The large volume of distribution may be due to low protein binding and probably to active transportation into tissue compartments [6].

### 7.3 Metabolism

Although the metabolism of 3-MMC is not fully disclosed, based on information obtained from the analysis by LC-HRMS of the pubic hair of a drug dealer who was charged by trafficking NPS, it is known that 3-methylephedrine and 3-methylnorephedrine are metabolites of the drug [16]. A hypothetical metabolic human pathway was proposed and presented in Fig. 4. The relevance of the metabolism for the pharmacological and toxicological profile of 3-MMC is yet to be revealed. Similar to 3-MMC, the metabolic pathway of 4-MMC is not fully known in humans [32]. However, the reduction and N-demethylation reactions are probably common metabolic pathways for these synthetic cathinones, since it is known that nor-mephedrone, nor-dihydro mephedrone, hydroxytolyl mephedrone, nor-hydroxytolyl mephedrone, and 4-carboxydihydromephedrone are metabolites of 4-MMC excreted in human urine [33].

### 7.4 Excretion

In pigs, the pharmacokinetics of 3-MMC appears to follow a one-compartment model [6]. The total clearance determined in this study represents more than the sum of liver and kidney blood flow (88 L/h) in pigs that weight 30-40 kg [6], which may signpost additional elimination sites or mechanisms besides hepatic and renal metabolism. The elimination half-life of 3-MMC was 0.83 h, corroborating the values achieved for total clearance and distribution volume. Most of the dose was excreted after 4 h of
administration, either when administered through injection, or orally [6]. The elimination rate constant of 3-MMC was 0.84 h\(^{-1}\) [6]. This rapid elimination rate may justify the short psychoactive effects and, consequently, the need to repeat oral administrations reported by users [8].

8. Toxicity

8.1 Lethal case reports

Few fatal intoxications have been reported due to the use of 3-MMC. The cases reported so far were thirteen and all occurred in Europe [8]. The available information about these cases is summarized in Table 4.

Only two deaths were attributed to 3-MMC alone. One of these deaths was reported in Italy in 2015 [34]. The other one was described by Bottinelli et al. [35] in 2016 and occurred in France. Therefore, the majority of the 3-MMC related deaths (eleven deaths out of thirteen) occurred with the co-ingestion of other drugs [7, 9, 10, 17, 34-37]. Of these, 5 deaths were attributed to drugs used for medical purposes [9, 10, 35, 36]. In the two deaths that involved 3-MMC alone, blood concentrations of 0.249 µg/mL [35] and 4.4 µg/mL [34] were reported. Because the number of fatal cases is relatively small, and because only two of these cases involved 3-MMC alone, it is not possible to draw any conclusion about potentially toxic and/or lethal 3-MMC concentrations. Also, postmortem findings are highly influenced by the circumstances of the intoxication, time elapsed from drug intake, and whether life support measures were adopted or not. For these reasons, the reported drug blood and/or tissue concentrations are highly discrepant among intoxicated individuals (Tables 4 and 5).

In Sweden, two deaths occurred from 2012 to 2014; both patients co-ingested 3-MMC with other drugs, namely amphetamines, buprenorphine and alcohol [7]. In the UK, one individual committed mechanical suicide under the influence of 3-MMC, venlafaxine, and amphetamine [38]. Suicide has already been associated with the use of other synthetic cathinones [39]. In Poland, five fatal cases involving 3-MMC were described [9]. The first case involved 3-MMC and MDMA. The second case involved 3-MMC and 5-(2-aminopropyl)benzofuran (5-APB). The third case also involved 3-MMC and 5-APB, but higher concentrations of the drugs were quantified in blood (Tables 4 and 5). The fourth case involved 3-MMC and 2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25I-NBOMe). The last
case involved 3-MMC and tramadol at therapeutic concentration [9]. In Norway, Karinen et al. [36] described the fatal intoxication of a young man with 3,4-dichloro-N-[(1-(dimethylamino)cyclohexyl)methyl]benzamide (AH-7921), 2-fluoromethamphetamine (2-FMA), 3-MMC, codeine, codeine-6-glucuronidie, and acetaminophen.

8.2 Mechanisms of toxicity
There are no studies elucidating the mechanisms of toxicity of 3-MMC. In the study conducted by Shimshoni et al. [6] in pigs, no changes in serum biochemical markers were found after the administration of 3-MMC. Some of these markers were cholesterol, creatinine, total protein, and urea. The authors also reported no drug-related mortality or morbidity and did not detect any gross pathological or abnormal histopathological findings [6]. The tissues analysed were the heart, skeletal muscles (diaphragm, intercostal, triceps, and others), lungs, pancreas, liver, kidney, spleen, brain and small intestine.

In the literature, the toxicological data regarding synthetic cathinones is scarce. It is expected that some of the mechanisms are similar to those of amphetamines, considering the similar structures and mechanisms of action [2]. It is well known that amphetamines cause hyperthermia, which can increase the formation of reactive species of oxygen and nitrogen species (ROS and RNS) [40]. As 3-MMC also causes hyperthermia, it is also likely to induce formation of ROS and RNS. Bäckberg et al. [7] described a fatal case where the patient was hyperthermic up to 20 h after administration (40.9 ºC), an effect that persisted even after sedation, external cooling and administration of cold fluids. The patient also had metabolic acidosis and rhabdomyolysis, which compromised his renal function. Six days after the admission to hospital, the patient died [7]. In comparison, the hyperthermia caused by MDMA is frequently responsible for complications contributing to fatal outcome, including rhabdomyolysis, acute renal failure, disseminated intravascular coagulation, multiple organ failure, and acidosis [41-43]. Some of these events were observed in the fatal case described by Bäckberg et al. [7]. This may suggest that 3-MMC shares some of the mechanisms of toxicity with MDMA.

8.3 Factors affecting the stimulant and toxicological effects
8.3.1 Dose
There are no studies in humans with 3-MMC that describe the relationship between the administered dose and the elicited stimulant/toxicological effects. The only study containing the dose information was reported by Bäckberg et al. [7] and describes the clinical features observed in patients tested positive for 3-MMC. Nevertheless, by virtue of the broad interval of doses mentioned (0.5–2 g), no associations between these and the reported symptoms could be established.

8.3.2 Blood concentration
The same applies to the blood concentrations found (Table 5). In the three-year review of Adamowicz et al. [27] mentioned above, the data collected from medical and police notes concerning 50 cases involving 3-MMC was divided in two groups: in the first group, information of the cases in which 3-MMC was detected alone was considered; in the second group, 3-MMC was detected along with other drugs. Regarding the first group, the blood concentration range observed for asymptomatic users was higher (0.01–0.2 µg/mL; mean 0.067 µg/mL) than that observed for individuals presenting 3-MMC-induced symptoms (0.01–0.02 µg/mL; mean 0.014 µg/mL). This was attributed to the fact that symptomatic individuals were mostly first time users, while the same was not observed for asymptomatic users. In the second group, the same tendency was observed (users with no symptoms: 0.001–0.2 µg/mL, mean 0.031 µg/mL and median 0.013 µg/mL; users with symptoms: 0.001–0.06 µg/mL, mean 0.02 µg/mL and median 0.07 µg/mL) but in this case results were more difficult to be interpreted, since polydrug abuse was at play. This will be further discussed below.

8.3.3 Route of administration
Stimulant and toxic effects are dependent on the route of administration. As mentioned above, the preferred route of administration is through insufflation, which may be explained by the low oral bioavailability [6]. Rapid onset of the effects and cultural preferences may also help explain the use of this administration route. After insufflation, the first effects appear between 20–30 min and the peak effect occur after 50 min, lasting up to 3–4 h. To prolong the effects, users repeat administration two or three times, every 2 h [9]. This is similar to 4-MMC, for which the first effects appear 15–45 min after administration, and last up to 4–5 h [44].
8.3.4 Polydrug abuse

Overall, 3-MMC is consumed with other drugs (Tables 3 and 4) and it is difficult to describe how this abuse pattern affects the induced stimulant and toxic effects [9] since the type of putative drug-drug interactions are unknown. Accordingly, most of the symptoms reported cannot be attributed to 3-MMC alone, although it is usual that polydrug users have less severe effects than those who only consume 3-MMC [27]. This can be explained due to the phenomenon of tolerance, as it is common that polydrug users are frequent drug abusers.

8.3.5 Interaction with therapeutic drugs

There are five cases described in the literature involving 3-MMC and therapeutic drugs, which were previously mentioned and are presented in Table 5. Although effects and pharmacokinetics of therapeutic drugs are in general well established, it is difficult to postulate on putative emerging interactions with 3-MMC because all too often there are also several drugs of abuse present. Contrary to the cases in which other types of drugs were detected, pharmaceuticals are present at very low levels. Adamowicz et al. [9] briefly described two fatal cases with 3-MMC and therapeutic drug interaction. Among the co-abused drugs were tramadol and Katelin, a dietary supplement characterized by high potassium chloride content (Table 5). Karinen et al. [36] reported a fatal case with 3-MMC, codeine, and acetaminophen. The man was prescribed a drug combination of codeine and acetaminophen (30 mg codeine/400 mg acetaminophen) after a minor traffic accident. He took 6 of these pills and some 3-MMC powder he bought online. The results from toxicological analysis of peripheral whole blood can be found in Table 5. Although codeine and acetaminophen were prescribed in therapeutic doses and low concentrations were found in blood, other non-therapeutic drugs were also taken and may have contributed for the fatality [36]. Other cases were documented describing concurrent administration of 3-MMC with acetaminophen, sildenafil and paroxetine [35] or with pseudoephedrine [10] (Table 5). In the latter case, the toxicological analysis of peripheral blood revealed the presence of 0.3 µg/mL of 3-MMC and 0.3 µg/mL of pseudoephedrine, along with 576 µg/mL of GHB (gamma-hydroxybutyric acid) [10]. As the concentration of pseudoephedrine is much lower than the concentration of 3-MMC and GHB, the author concluded that it was likely that the death occurred because of the interaction
of 3-MMC and GHB. It was hypothesized that the trace of pseudoephedrine was derived either from a clinical treatment or from the illicit manufacture of 3-MMC, since pseudoephedrine is also a precursor in methamphetamine and methcathinone synthesis [10].

8.3.6 Environmental conditions
When the use of the drug occurs in nightclubs, where the atmosphere is hot and crowded and deprived of ventilation, it is expected much more severe detrimental effects, as these conditions may harshly aggravate the hyperthermia and diaphoresis elicited by 3-MMC [7]. Accordingly, a body temperature as high as 40.9 °C was observed in an individual who took the drug in a hot environment. This is consistent with what is known for the related drug MDMA. Studies in rats evidenced that when the environmental temperature was below 22 °C animals tended to develop hypothermia, and when the temperature was above 28 °C, the elicited hyperthermia became life-threatening [45].

9. Drive under the influence of 3-MMC
Since 3-MMC has been often detected in the driving under influence of drugs (DUID) monitoring [8, 9, 22], this drug represents a major concern for the road safety policy in several countries, posing a serious risk to the user and, eventually, other passengers and pedestrians involved. In Germany, Maas et al. [15] described the case of a user driving under the influence of methadone, 3-MMC, and lorazepam, who presented deficient concentration, delayed reaction time, problems with balance and coordination, impaired fine motor skills, washed out pronunciation, and disorientation. The user still showed signs of drug influence approximately 8h later. In Poland, Adamowicz et al. [9] reviewed 70 cases either related to traffic accidents (4) or other DUID cases (66) in which 3-MMC was involved and categorised these occurrences in two groups; in the first one, 3-MMC was the only substance present, while in the second there was co-administration of other drugs [9]. In the first group, there were 13 asymptomatic cases and 6 cases of drivers who presented symptoms including gaiety, verbosity, stuttering, fatigue, agitation, aggression, uncoordinated movements and tachycardia. The 3-MMC blood concentrations were in the range of 0.003–0.171 µg/mL (mean 0.046 µg/mL and median 0.012 µg/mL) and 0.011–0.03 µg/mL (mean 0.025 µg/mL and median 0.024 µg/mL), respectively. In the second
group, the authors observed 28 cases of drivers presenting no symptomatology, although 3-MMC was present at concentrations between \(<0.001–0.163 \mu g/mL\) (mean 0.036 \(\mu g/mL\) and median 0.013 \(\mu g/mL\)) alongside with amphetamine, MDMA, benzoylcegonine, THC, clonazepam, among others. In the 23 symptomatic cases observed, 3-MMC at \(<0.001–0.077 \mu g/mL\) (mean 0.023 \(\mu g/mL\) and median 0.012 \(\mu g/mL\)) mainly co-occurred with amphetamine and THC; and the symptoms again included anxiety, depression, disorientation, verbosity, slurred speech, strange behaviour, unsteady gait, staggering and tachycardia. Some drivers also presented reddened facial skin. The data presented in this study does not reveal a correlation between the 3-MMC concentration and the observed symptoms [9]. This may be a result of the development of tolerance, since asymptomatic individuals who presented higher drugs concentration in blood are likely frequent users [9].

10. Conclusions
With the increase in consumption and the lack of toxicological studies on 3-MMC, its toxicological assessment has become mandatory. Indeed, by virtue of the scarce information on the drug, there is an immense scope to explore: it is of great importance to clearly describe and report the observed toxic effects on diverse target organs, as consistent published data on the subject is absent; to investigate the mechanisms underlying the observed effects; to reveal metabolic pathways and the relevance of 3-MMC metabolism for the psychological and toxicological effects of the drug. In addition, it is also highly relevant to study pharmacokinetics in different animal models and to scrutinize the signalling pathways triggering the known detrimental toxicological effects.

Declaration of interests
The authors have no competing interests to declare.

Acknowledgments
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Author Contribution Statement

All the authors substantially contributed to the study conception and design, and drafted or revised the article for intellectual content. Authors' individual contributions are outlined below:

Bárbara Ferreira - Literature search and writing of the original draft

Diana Dias da Silva – Conceptualization and writing of the original draft

Félix Carvalho - Funding acquisition, project administration and review & editing of the original draft

María de Lourdes Bastos - Funding acquisition, project administration and review & editing of the original draft

Helena Carmo – Supervision and review & editing of the original draft
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Figure Legends

Fig. 1 Chemical structures of amphetamine, natural cathinone, and synthetic cathinone derivatives.
Fig. 2 Crystals and powder of 3-methylmethcathinone (3-MMC) are sold on-line as research chemicals.
Fig. 3 Synthesis of 3-methylmethcathinone (3-MMC). EtMgBr – ethyl magnesium bromide; PCC/Silica gel – pyridinium chlorochromate on silica gel; HBr – hydrobromic acid; H₂O₂ – hydrogen peroxide; MeNH₂ – methylamine; HCl – hydrogen chloride. Adapted from Power et al. [12].
Fig. 4 Hypothetic metabolism of 3-methylmethcathinone (3-MMC) into 3-methylnorephedrine through β-keto-reduction [1] followed by N-demethylation [2] into 3-methylnorephedrine. Adapted from Frison et al. [16].
### Tables

**Table 1 Physicochemical properties of 3-methylmethcathinone (3-MMC or metaphedrone) hydrochloride salt.** Adapted from Shimshoni et al. [6] and WHO [8]

<table>
<thead>
<tr>
<th>Properties</th>
<th>3-MMC (hydrochloride salt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C_{11}H_{15}NO.HCl</td>
</tr>
<tr>
<td>Molecular mass (g/mol)</td>
<td>213.7</td>
</tr>
<tr>
<td>Melting point (°C)</td>
<td>193.2</td>
</tr>
<tr>
<td>Boiling point (°C) (at 760 mm Hg)</td>
<td>280.5</td>
</tr>
<tr>
<td>pKa</td>
<td>7.84</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in water</td>
</tr>
<tr>
<td></td>
<td>Slightly soluble in ethanol, dimethyl sulfoxide, and dimethyl formamide</td>
</tr>
<tr>
<td>Partition coefficient (cLogP)</td>
<td>1.86</td>
</tr>
<tr>
<td>Chemical Abstracts Service (CAS)number</td>
<td>1246816-62-5</td>
</tr>
<tr>
<td>Other chemical names</td>
<td>3-Methylmethcathinone;</td>
</tr>
<tr>
<td></td>
<td>3-Methyl-N-methylcathinone;</td>
</tr>
<tr>
<td></td>
<td>Metaphedrone;</td>
</tr>
<tr>
<td></td>
<td>2-(Methylamino)-1-(3-methylphenyl)-1-propanone</td>
</tr>
</tbody>
</table>
Table 2 Patterns of consumption of 3-methylmethcathinone (3-MMC or metaphedrone), as evaluated in individuals confirmed positive for drug abuse.

<table>
<thead>
<tr>
<th>Year</th>
<th>Country/Location</th>
<th>n</th>
<th>Age (years)</th>
<th>Individuals consuming 3-MMC (%)</th>
<th>Consumed dose (g)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012 – 2013</td>
<td>Budapest</td>
<td>1959</td>
<td>18 – 50</td>
<td>1.0</td>
<td></td>
<td>[18]</td>
</tr>
<tr>
<td></td>
<td>Csongrád Country, Hungary</td>
<td>472</td>
<td></td>
<td>5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012 – 2014</td>
<td>Sweden</td>
<td>786</td>
<td>17 – 49 (mean 25.5; median 24)</td>
<td>6.4</td>
<td>0.5 – 2</td>
<td>[7]</td>
</tr>
<tr>
<td>2012 – 2014</td>
<td>Poland</td>
<td>112</td>
<td>16 – 50 (mean 25.4; median 24.5)</td>
<td>44.6</td>
<td></td>
<td>[27]</td>
</tr>
<tr>
<td>2014</td>
<td>Slovenia</td>
<td>249</td>
<td>15 – 40 (^1) (mean 23)</td>
<td>67.9</td>
<td>1.5</td>
<td>[22]</td>
</tr>
<tr>
<td>2010 – 2016</td>
<td>Southern Germany</td>
<td>81</td>
<td>17 – 49 (median 34)</td>
<td>16.0</td>
<td></td>
<td>[24]</td>
</tr>
</tbody>
</table>

\(^1\) Mostly students
Table 3 Case reports of non-fatal intoxications involving 3-methylmethcathinone (3-MMC or metaphedrone).

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Cases (n)</th>
<th>Sex/Age (years)</th>
<th>Intoxication symptoms</th>
<th>Drug Concentration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012–2014</td>
<td>Sweden</td>
<td>50</td>
<td>M (n = 38); F (n = 12)/17–49</td>
<td>Tachycardia (\geq 100/\text{min}); Agitation; Hypertension (systolic blood pressure (\geq 140) mmHg); Reduced level of consciousness (RLS (&gt;2)); Dilated pupils; Hallucinations; Hyponatremia (136 mmol sodium/L); Diaphoresis; Seizures; Significant hyperthermia (39 °C); Rhabdomyolysis (25 IU CK/L, 3000 μg myoglobin/L)</td>
<td>0.002–1.5 µg/mL (mean 0.261 µg/mL; median 0.091 µg/mL) of 3-MMC(^c); 0.007–290 µg/mL (mean 3.58 µg/mL; median 3.05 µg/mL) of 3-MMC(^a)</td>
<td>[7]</td>
</tr>
<tr>
<td>2012–2014</td>
<td>Poland</td>
<td>112</td>
<td>M (n = 102); F (n = 10)/16–50 (mean 25.4; median 24.5)</td>
<td>Verbosity; Slurred speech; Strange behaviour; Unsteady gait; Staggering</td>
<td>&lt; 0.001–1.6 µg/mL (mean 0.096 µg/mL; median 0.013 µg/mL) of 3-MMC(^b)</td>
<td>[27]</td>
</tr>
<tr>
<td>2013–2015</td>
<td>Poland</td>
<td>95</td>
<td>M (n = 89); F (n = 6)/17–50 (mean 25.9; median 26)</td>
<td>Gaiety; Verbosity; Stuttering; Fatigue; Agitation; Aggression; Uncoordinated movements; Tachycardia (100 bpm)</td>
<td>0.003–0.2 µg/mL (mean 0.051 µg/mL; median 0.091 µg/mL) of 3-MMC(^b); 7–435 ng/mL of amphetamine; 257–646 ng/mL of MDMA; 20–156 ng/mL of benzoylecgonine; &lt;1–7.2 ng/mL of THC; 4 ng/mL of clonazepam</td>
<td>[9]</td>
</tr>
<tr>
<td>2015–2016</td>
<td>France</td>
<td>3</td>
<td>F/22</td>
<td>Confusion; Somnolence; Miosis; GS = 10</td>
<td>0.3 µg/mL of 3-MMC(^c); 0.02 µg/mL of 5-MAPB(^b); 0.1 µg/mL of methadone</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M/35</td>
<td>Agitation; Hypertension; Chest pain; Tachycardia</td>
<td>0.007 µg/mL of 3-MMC(^c); 2.4 µg/mL of 3-MMC(^u)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M/29</td>
<td>Hallucinations; Tachycardia</td>
<td>0.2 µg/mL of 3-MMC(^b)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3 Case reports of non-fatal intoxications involving 3-methylmethcathinone (3-MMC or metaphedrone) (continuation).

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Cases (n)</th>
<th>Sex/Age (years)</th>
<th>Intoxication symptoms</th>
<th>Drug Concentration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015–2016</td>
<td>France</td>
<td>3</td>
<td>M/23</td>
<td>Seizures; GS = 3</td>
<td>1.6 μg/mL of 3-MMC; 0.9 μg/mL of 4-MEC; 1.2 μg/mL of MXE; 141 μg/mL of 3-MMC; 61 μg/mL of 4-MEC; 39 μg/mL of MXE</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M/37</td>
<td>Agitation; Mydriasis; Tachycardia</td>
<td>0.06 μg/mL of 3-MMC; 0.2 μg/mL of 4-MEC; 0.01 μg/mL of MEX; 0.1 μg/mL of MDMA; 13 μg/mL of 3-MMC; 85 μg/mL of 4-MEC; 0.9 μg/mL of MEX; 5.6 μg/mL of MDMA; 0.3 μg/mL of MDA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M/30</td>
<td>Coma; Miosis; Bradypnea; GS = 3-5</td>
<td>0.2 μg/mL of 3-MMC; 200 μg/mL of GHB; 41.6 μg/mL of 3-MMC; 685 μg/mL of GHB</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Germany</td>
<td>1</td>
<td>M/34</td>
<td>Deficient concentration; Delayed reaction time; Problems with balance and coordination; Impaired fine motor skills; Washed out pronunciation; Disorientation</td>
<td>0.1 μg/mL of methadone; 0.006 μg/mL EDDP; 0.03 μg/mL of lorazepam; 0.04 μg/mL of 3-MMC</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>Italy</td>
<td>1</td>
<td>M</td>
<td></td>
<td>0.03 μg/mL of 3-MMC</td>
<td></td>
</tr>
<tr>
<td>2014–2016</td>
<td>Germany</td>
<td>2</td>
<td>F/26</td>
<td>Depressive mood; Pupil with slow reaction to light</td>
<td>0.04 μg/mL of 3-MMC</td>
<td></td>
</tr>
</tbody>
</table>

RLS – Reaction level scale; CK – Creatine kinase; EDDP – 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; GS – Glasgow score; 5-MAPB – 5-(2-Methylaminopropyl)benzofuran; 4-MEC – 4-Methylethcathinone; MXE – Methoxetamine; MDMA – 3,4-Methylenedioxymethamphetamine; MDA – 3,4-Methylenedioxyamphetamine; Bpm – beats per minute

| * | Serum; | * | Urine; | * | Plasma; | * | Pubic hair |
Table 4 Deaths related to 3-methylmethcathinone (3-MMC or metaphedrone).

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Cases (n)</th>
<th>Sex/Age (years)</th>
<th>Cause of death/ autopsy findings</th>
<th>Postmortem toxicological analysis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012–2014</td>
<td>Sweden</td>
<td>2</td>
<td>M</td>
<td>Polydrug abuse</td>
<td>3-MMC: 0.002 μg/mL (s); 0.09 μg/mL (u). Small concentration of ethanol metabolites (u).</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M/25</td>
<td>Polydrug abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>UK</td>
<td>1</td>
<td></td>
<td>Mechanical suicide</td>
<td>1.1 μg/mL of 3-MMC (^{fb}); 1.6 μg/mL of venlafaxine (^{fb}); 2.8 μg/mL O-desmethylvenlafaxine (^{fb})</td>
<td>[38]</td>
</tr>
<tr>
<td>2013–2015</td>
<td>Poland</td>
<td>4</td>
<td>M</td>
<td>Polydrug abuse</td>
<td>&lt; 0.001 μg/mL of 3-MMC; 0.03 μg/mL of MDMA</td>
<td>[9]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Polydrug abuse</td>
<td>0.02 μg/mL of 3-MMC; 0.1 μg/mL of 5-APB (^{1}); 3.4 mg/g of Katelin (^{s})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multiple organ failure/ Acute</td>
<td>0.01 μg/mL of 3-MMC (^{b}); 0.003 μg/mL of 25I-NBOMe (^{b})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>respiratory failure caused by</td>
<td>0.003 μg/mL of 3-MMC (^{b}); 0.6 μg/mL of tramadol (^{b})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>massive pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>Norway</td>
<td>1</td>
<td>M/early twenties</td>
<td>Polydrug abuse/Oedematous lungs</td>
<td>0.002 μg/mL of 3-MMC (^{pwb}); 0.4 μg/mL of AH-7921 (^{pwb}); 0.4 μg/mL of codeine (^{pwb}); 0.8 μg/mL C6G (^{pwb}); 19 μg/mL of acetaminophen (^{pwb}); 0.007 of μg/mL 2-FMA (^{pwb})</td>
<td>[36]</td>
</tr>
<tr>
<td>2014</td>
<td>Poland</td>
<td>1</td>
<td>M/20</td>
<td>Polydrug abuse</td>
<td>1.6 μg/mL of 3-MMC (^{b}); 5.6 μg/mL of 5-APB (^{b})</td>
<td>[17]</td>
</tr>
<tr>
<td>2015</td>
<td>Italy</td>
<td>1</td>
<td>3-MMC intoxication</td>
<td></td>
<td>4.4 μg/mL of 3-MMC (^{b})</td>
<td>[34]</td>
</tr>
</tbody>
</table>
Table 4 Deaths related to 3-methylmethcathinone (3-MMC or metaphedrone) (continuation).

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Case (n)</th>
<th>Sex/Age (years)</th>
<th>Cause of death/ Autopsy findings</th>
<th>Postmortem toxicological analysis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>France</td>
<td>2</td>
<td>M/thirties</td>
<td>Polydrug abuse</td>
<td>0.08 µg/mL of 3-MMC b; 180 µg/mL of alcohol b; 0.1 µg/mL of paracetamol b; 0.1 µg/mL of paroxetine b; 0.08 µg/mL of sildenafil b; 0.1 µg/mL of 4-MEC b</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-MMC intoxication 0.2 µg/mL of 3-MMC b</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>France</td>
<td>1</td>
<td>M/69</td>
<td>Polydrug abuse</td>
<td>3-MMC: 0.33 µg/mL pb; 0.9 µg/mL cb; 29.0 µg/mL u; 1.5 µg/mL gc; 0.6 µg/mL lb; 206.7 ng/mg h; GHB 1: 576 µg/mL pb; 630 µg/mL cb; 719 µg/mL u; 909 µg/mL hi; 96.3 ng/mg h. Pseudoephedrine: 0.03 µg/mL pb; 0.08 µg/mL cb; 1.1 µg/mL u; 0.1 µg/mL gc; 0.05 µg/mL lb; 0.2 ng/mg h.</td>
<td>[10]</td>
</tr>
<tr>
<td>2016</td>
<td>France</td>
<td>1</td>
<td>M/32</td>
<td>3-MMC intoxication</td>
<td>3-MMC: 0.2 µg/mL pb; 0.6 µg/mL cb; 3.0 µg/mL vh; 29.7 µg/mL Lu; 1.3 µg/mL lb. GHB: 35.7 µg/mL pb; 25.0 µg/mL cb; 8.8 µg/mL u; 12.4 µg/mL hi.</td>
<td>[37]</td>
</tr>
<tr>
<td>2014–2015</td>
<td>Germany</td>
<td>1</td>
<td></td>
<td>Cardiac arrest/ Cerebral oedema and brain death</td>
<td></td>
<td>[24]</td>
</tr>
</tbody>
</table>

3-MMC – 3-Methylmethcathinone; MDMA – 3,4-Methylenedioxymethamphetamine; 5-APB – 5-(2-Aminopropyl)benzofuran; Katelin – dietary supplement characterized by high potassium chloride content; 25I-NBOMe – 2-(4-Iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine; AH-7921 – 3,4-Dichloro-N-[[1-(dimethylamino)cyclohexyl]methyl]obenzamide; C6G – Codeine-6-glucuronide; 2-FMA – 2-Fluoromethamphetamine; 4-MEC – 4-Methylethcathinone; GHB – γ-Hydroxybutyric acid;

pwb Peripheral whole blood; pb Blood; pb Peripheral blood; s Stomach; cb Cardiac blood; u Urine; gc Gastric content; bl Bile; h Hair; fb Femoral blood; vh Vitreous humor
Table 5 Blood concentrations of 3-methylmethcathinone (3-MMC or metaphedrone) in fatal and non-fatal intoxications.

<table>
<thead>
<tr>
<th>Dose (g)</th>
<th>Concentration (µg/mL)</th>
<th>Post-mortem concentration (µg/mL)</th>
<th>Intoxication</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.002</td>
<td>Fatal</td>
<td></td>
<td>[36]</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>Fatal</td>
<td></td>
<td>[17]</td>
</tr>
<tr>
<td>0.5–2</td>
<td>0.002–1.5 (mean 0.261; median 0.091)</td>
<td>Non-fatal</td>
<td></td>
<td>[7]</td>
</tr>
<tr>
<td>0.04</td>
<td></td>
<td>Non-fatal</td>
<td></td>
<td>[15]</td>
</tr>
<tr>
<td>&lt; 0.001–1.6 (mean 0.096; median 0.013)</td>
<td>Non-fatal</td>
<td></td>
<td>[27]</td>
<td></td>
</tr>
<tr>
<td>0.003–0.2 (mean 0.051; median 0.019)</td>
<td>Non-fatal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
<td>Fatal</td>
<td></td>
<td>[9]</td>
</tr>
<tr>
<td></td>
<td>0.02</td>
<td>Fatal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.01</td>
<td>Fatal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.003</td>
<td>Fatal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.02</td>
<td></td>
<td>Non-fatal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>Fatal</td>
<td></td>
<td>[10]</td>
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*The only drug reported to be involved was 3-methylmethcathinone (3-MMC).