Mephedrone (4-methylmethcathinone; 'meow meow'); chemical, pharmacological and clinical issues

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Abstract 248 words

Recently, those substances deriving from the active ingredient of the Khat plant, cathinone, have been rising in popularity. Indeed, 4-methylmethcathinone (mephedrone; ‘Meow Meow’ and others) has been seen by some as a cheaper alternative to other classified recreational drugs. We aimed here at providing a state-of-the-art review on mephedrone history and prevalence of misuse; chemistry; pharmacology; legal status; product market appearance; clinical/management; and related fatalities. Because of the limited evidence, some of the information here presented has been obtained from user reports/drug users’ orientated websites.

Most common routes for mephedrone recreational use include insufflation and oral ingestion. It elicits stimulant and empathogenic effects similar to amphetamine, methylamphetamine, cocaine and MDMA. Due to its sympathomimetic actions, mephedrone may be associated with a number of both physical and psychopathological side effects. Recent preliminary analysis of recent UK data carried out in 48 related cases have provided positive results for the presence of mephedrone at post mortem.

Within the UK, diffusion of mephedrone may have been associated with an unprecedented combination of a particularly aggressive online marketing policy and a decreasing availability/purity of both ecstasy and cocaine. Mephedrone has been recently classified in both the UK and in a number of other countries as a measure to control its availability. Following this, a few other research

psychoactives have recently entered the online market as yet unregulated substances that may substitute for mephedrone. Only international collaborative efforts may be able to tackle the phenomenon of the regular offer of novel psychoactive drugs.

Key words: mephedrone; meow meow; cathinones; drug misuse; drug related deaths; psychoactive drugs.

INTRODUCTION

Mephedrone (4-methylmethcathinone; 'Plant Food', 'Meow Meow', 'Miaow', 'Drone', 'Meph', 'Bubbles', 'Spice E', 'Charge', 'M-Cat', 'Rush', 'Ronzio', 'Fiskrens' and 'MMC Hammer') is the most popular of the cathinone derivatives, which also include butylone; methylone, and remaining compounds (ACMD 2010; Morris 2010). It has been readily available for purchase both online and in head shops and its circulation has been promoted by aggressive web-based marketing (Deluca et al, 2009; Mephedrone2you 2010; National Treatment Agency 2010).

Mephedrone is a psychoactive research chemical that elicits stimulant and empathogenic effects similar to amphetamines, methylamphetamine, cocaine and MDMA (Winstock et al 2010a). It has drawn wider attention from the media since it has been allegedly linked to a number of fatalities. As we write, only few formal papers and experimental/clinical data have been published (Dargan et al 2010; Winstock et al 2010a; Winstock et al 2010b). Some of the information contained in this review has been obtained from user reports and drug users' orientated websites, again highlighting the lack of peer reviewed resources. Given the limited information available, we aimed here at providing a state-of-the-art review on mephedrone chemical, pharmacological and clinical issues.

HISTORY AND PREVALENCE OF MISUSE

In 1929, Saem de Burnaga Sanchez first described the synthesis of mephedrone. However, khat-extracted cathinones first appeared in Israel in early 2000's, locally named as 'Hagigat' (Urquhart 2009), eventually outlawed following a large number of hospitalisations caused by its exposure (Bentur 2008). As a result of the ban, chemists began altering the chemical structure of cathinone to synthesize related unscheduled compounds. First online reference to mephedrone reportedly occurred in May 2003 (Power 2009), but both its availability for online purchase (Camilleri et al 2010; Roussel et al 2009) and related popularity (Deluca et al 2009) started in 2007. Data collected by the European Monitoring Centre for Drugs and Drug Addiction show that over the first quarter of 2010 there have been detections in some 20 EU Member States, with most of them reporting small to medium-size seizures (Europol-EMCDDA 2010).

Although not well known in the USA, 4-methylmethcathinone appears to be particularly popular in the UK (Brandt et al 2010a; Mephedrone2you 2010). During the second quarter of 2009, the Forensic Science Service received submissions of three times as many samples of mephedrone for analysis than it had in the previous 12-month period (ACMD 2010; Ghodse et al 2010). Since mephedrone appeared only very recently on the market, it does not feature in most drug use household surveys, and it is uncertain how many people present with a history of mephedrone misuse. Most available data originate from self-reported surveys and small focus group research. Main settings of use might be nightclubs, parties and people's home (Newcombe 2009). A research project led

by the National Addiction Centre in London with 2,295 readers of the dance magazine ‘Mixmag’ disclosed that 41.7% of surveyed people had ever tried 4-methylmethcathinone and 33.2% had used during last month, making it the sixth most popular drug among clubbers, after tobacco, alcohol, cannabis, ecstasy and cocaine. Cathinone derivative methylone was mentioned as well in the survey (Winstock et al, 2010b). Dargan et al (2010) assessed both prevalence and frequency of use of mephedrone. Data was collected using a questionnaire survey in schools, colleges and universities in the Tayside area of Scotland in February 2010. Some 1006 individuals completed the survey and 205 (20.3%) reported previous use of mephedrone; 23.4% reported using only using mephedrone on one occasion previously, and 4.4% reported daily use. A total of 48.8% of users sourced mephedrone from street level dealers and 10.7% from the Internet. Although both the Mixmag and Scottish schools surveys are limited by the nature of sampling technique and target populations, the heightened interest in mephedrone (National Treatment Agency 2010) might be readily testified by the rise in number of both telephone inquiries and visits to both the TOXBASE and FRANK websites (ACMD 2010).

Mephedrone appearance on the UK market may have been associated with an unprecedented decreasing purity of both MDMA and cocaine (Hand and Rishiraj 2009; Fleming 2010; Measham et al 2010; National Treatment Agency 2010). Similar observations have been recently reported from the Netherlands (Brunt et al, 2010). As a consequence, drug users may have switched to mephedrone, being allegedly cheaper and more powerful than the currently available

‘traditional’ stimulants (Deluca et al 2009). Moreover, recent changes in the attitudes of drug users, as well information-sharing and marketing through the Internet, are likely to have played a significant role. Ready availability of mephedrone may well have boosted its diffusion and prior to its ban many surveyed people thought 4-methylmethcathinone not to be harmful because of its appealing legal status (Daly 2010; Ramsey et al 2010). This combination of circumstances has been massively capitalized on by suppliers who may conceivably have made huge profits by promoting the drug through an aggressive e-commerce advertising policy and by arranging a widespread delivery system (Power 2010; Freepressindex 2010; Mephedrone2you 2010). Paradoxically, online newspaper articles about mephedrone contained banners pointing towards drug vendors and some editorialists have indicated mephedrone as an example of the future of drug dealing (Power 2009). One could also wonder about the possible role the media has played in promoting mephedrone use (Davey et al 2010). From this point of view, Measham and colleagues (2010) have referred to the conceptualization of mephedrone in the media as a ‘moral panic’, and as such this may have obscured the potential for accurate and valuable safety information to be transmitted and received on a large scale.

Immediately after the mephedrone ban, novel compounds have already appeared on the horizon, with molecules such as naphyrone (also known as naphthylpyrovalerone, ‘Energy 1’ or ‘NRG-1’) and MDAi (5,6-methylendioxy-2-aminoindane) representing two of the emerging research chemicals set to replace mephedrone as alternative psychoactives. In fact, they are marketed and

advertised with modalities similar to those referring to mephedrone up to a few months ago (Townsend 2010). Interestingly, some of these products have been shown to contain mephedrone and/or MDPV (Methylenedioxypyrovalerone; Brandt et al 2010b).

CHEMICAL CHARACTERISTICS:

Mephedrone is a semi-synthetic compound belonging to the chemical class of cathinone derivatives (or substituted cathinones). Cathinone is a natural amphetamine-like alkaloid found in the fresh leaves and stems of the African shrub Catha edulis (Khat; Kalix 1992). The systematic name of mephedrone is 2-(methylamino)-1-(p-tolyl)propan-1-one(2S)-2-(methylamino)-1-(4-methylphenyl)propan-1-one, in accordance with the International Union of Pure and Applied Chemistry (IUPAC). Different acronyms include 1-(4-methylphenyl)-2-methylaminopropan-1-one, 2-methylamino-1-p-tolylpropan-1-one, 4-methylmethcathinone, 4-MMC, and MMCAT. The molecular formula and mass are $C_{11}H_{15}NO$ and 177.242 g/mol, respectively (Chemspider 2010; Kalix 1992; Pubchem 2010). The structure of mephedrone is shown in Figure 1 where it differs from cathinone by methylation of the amino group and the benzene ring present (Gustaffson and Escher 2009; Osorio-Olivares et al 2003). The cathinones are beta keto derivatives of phenethylamines (Figure 1), and hence analogues of amphetamines (Chemspider 2010). Since they are mainly synthetic

in origin, beta-keto amphetamines are also known as ‘bk designer drugs’. Each of the phenethylamine compounds has a parallel cathinone analogue. For example, methcathinone is the cathinone anologue of methylamphetamine (ACMD 2010).

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Figure 1. Mephedrone and related structures

Like other cathinone derivatives, mephedrone possesses a single chiral centre thereby existing in two enantiomeric forms, (*S*)- and (*R*)-mephedrone (Europol-EMCDDA 2010; Gibbons and Zloh 2010). For cathinone, the S(-) form is more potent than the *R*(-) enantiomer, and this may be similar for mephedrone. The synthesis of (*S*)-4-methylcathinone, an (S)-mephedrone precursor, has been carried out *via* Friedel-Crafts acylation as shown in Figure 2 (Osorio-Olivares et al 2003) 2). Further methylation of the amino group would yield (*S*)-mephedrone.

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Figure 2. Stereoselective synthesis of (*S*)-4-methylcathinone

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It is relatively easy to produce mephedrone in non-professional laboratories (Figure 3) via bromination of 4-methylpropiophenone followed by reaction with methylamine or by oxidation of 4-methylephedrine (Archer 2009; Europol-EMCDDA 2010). Both reactions would result in a mixture of *R*- and *S*-mephedrone. However, a stereoselective synthesis in the latter is possible using a single enantiomeric form (Lee et al 2007) of 4-methylephedrine (Europol-EMCDDA 2010).

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Figure 3. Synthesis of mephedrone

PHARMACOLOGY

Some cathinone derivatives are currently under active research as a promising class of monoamine uptake inhibitors (Meltzer et al 2006). However, only little is known about the pharmacology of 4-methylmethcathinone. Given cathinone derivatives affiliation to beta-ketoamphetamines, mephedrone is expected to act as a central nervous system stimulant by promoting the release of monoamine neurotransmitters and likely inhibiting their reuptake (Kalix 1990; Feyiisa and Kelly 2008). Indeed, in vitro studies on the effects of the cathinone derivatives

methcathinone and methylone confirm that the main mechanism of action is very similar to that of amphetamine, therefore being characterized by a predominant action on plasma membrane catecholamine transporters (Cozzi et al, 1999). Both amphetamines and cathinones bind to noradrenalin, dopamine and serotonin transporters (Nagai et al 2007), each of them differing from each other by its relative binding potency. In particular, the presence of the ring substituent on the phenethylamine core modifies the pharmacological properties by giving the compound some MDMA-like effects, whereas amphetamines and cathinone derivatives without ring substituents exert mostly stimulant effects (Europol-EMCDDA 2010). Cathinones' potencies are mostly lower than those of amphetamines, as beta-keto amphetamines show a reduced ability to cross the blood-brain barrier due to the presence of the beta group (Nagai et al 2007; Gygi et al 1996).

N-demethylation to the primary amine, reduction of the keto moiety to the respective alcohol, and oxidation of the tolyl moiety to the corresponding alcohols and carboxylic acid is the major metabolic pathway for mephedrone, followed by N-dealkylation. Intake of both mephedrone and other beta-keto-amphetamines can be detected with appropriate urine testing technology (Meyer et al 2010; Zaitsu et al 2009).

LEGAL STATUS

At the time of writing, mephedrone is not under a consistent international control. In fact, misuse of mephedrone has spread very quickly in a relatively short period of time, notably arising in popularity among drug users (see Table 1; under supplementary material). In the UK, where mephedrone has been greatly drawing both mass media and Government attention, the Advisory Council on the Misuse of Drugs has published a report on the cathinone derivatives, recommending their inclusion in the Misuse of Drugs Act 1971 under Class B. As a result, mephedrone was made a controlled drug (class B) on the 16th April 2010 (ACMD, 2010). It may be of interest that control in some countries (e.g. Finland) has been by use of legislation other than the Misuse of Drugs Act or equivalent measures (see Table 1; under supplementary material).

Although in a way similar to many other recreational drugs 4-methylmethcathinone has been specifically synthesized to avoid existing drug misuse laws (BBC News 2009; Deluca et al 2009; Financiarul online 2010), many synthetic 'legal highs' may not be legal. In fact, active ingredients in legal highs purchased from Internet-based suppliers do not remain consistent over time, hence increasing the risk of individuals purchasing a 'legal high' that contains a controlled drug (Ramsey et al, 2010). Furthermore, even if they have no history of previous use as drugs, specific psychoactive substances may still be liable to control under the Medicines Act. However, labelling is likely to be the key to better understand the phenomenon. In fact, a number of recreational psychoactive drugs available for online purchase, including mephedrone, are claimed to be 'plant feeders', 'bath salts' and 'not for human consumption'

(Mephedrone2you 2010), and prosecution as such may be difficult (Winstock and Ramsey, 2010). Many online suppliers' sites implicitly however suggest its use as a drug, referring to the rave and party culture in the website graphic design and/or providing the customers with ambiguous reviews written by self-styled gardeners (Mephedrone.com 2010). It is of concern that, despite the banning of mephedrone, little may indeed prevent suppliers from using the same marketing approach for novel and shortly forthcoming compounds (Brandt et al 2010a).

Finally, it is worth noting that in March 2010 the EMCDDA and Europol submitted a joint report on mephedrone (Europol-EMCDDA 2010) to the Council of the EU, the European Commission and the European Medicines Agency (EMA), presenting the case for the forthcoming formal risk assessment of the drug.

MARKET AND COMMERCIAL APPEARANCE

Mephedrone occurs as a white, sometimes off-white or slightly yellowish, powder or fine crystals. Less frequently, it is marketed as capsules or tablets of various colours, shape, and thickness, with or without a logo. Although mainly sold in powder and crystal forms, mephedrone may be commercially available in tablets and included within vegetable-based capsules. It has been reported that mephedrone is sometimes sold in some countries as either ecstasy or cocaine (Deluca et al 2009; ABC News 2008). Furthermore, it may be found to be mixed with some adulterants, such caffeine, paracetamol and even cocaine, amphetamine and ketamine (Camilleri et al 2010).

ROUTES OF ADMINISTRATION; DOSAGE; USE IN COMBINATION WITH OTHER DRUGS

Most common routes for recreational use include insufflation (snorting) and oral ingestion. Because of its solubility in water, mephedrone is reportedly used by rectal administration (dissolved in an enema or within gelatine capsules) as well, or injected intravenously. Insufflation is likely to be the most common modality. When snorted, mephedrone elicits its effects within a few minutes, with the peak being reached in less than 30 minutes followed by a rapid comedown. According to online users' advice, mephedrone dosage for snorting may range between 25mg and 75mg, with the lower threshold being at 5-15mg and with a level in excess of 90mg to be considered a high dosage (Sumnall and Wooding 2009). Dosing is more frequent when taken intranasally; this route is allegedly associated with greater abuse liability than the oral route (Winstock et al, 2010).

Other typical methods of intake include oral administration, through ingestion of capsules or tablets; swallowing mephedrone powder wrapped up in cigarette paper ('bombing'); or mixed with water. On average, the most common oral dosages are higher than the snorting ones (Sumnall and Wooding 2009), being in the range between 150mg and 250mg. Time of onset may be of 45 minutes-2 hours, and may vary in association with the amount of food contained in the stomach. Because of this, users suggest to take mephedrone on an empty

stomach. With oral administration, psychoactive effects may last longer (up to 2-4 hours); side effects might be milder and the urge to re-dose less pressing. Some consumers exploit both insufflation and oral ingestion in combination to achieve both faster onset and long-lasting effects (Deluca et al 2009). With respect to oral ingestion, users report that rectal administration is characterized by faster onset of the effects and requires lower doses, e.g. 100mg on average (Deluca et al 2009).

Although not typically advised, because this may increase the drug addictive liability levels (Deluca et al 2009), mephedrone may also be injected either intramuscularly (Wood et al, 2010a) or intravenously (IV), at 1/2 or 2/3 of the oral dose (Deluca et al 2009). This method of intake appears to be fairly well known in Romania, where mephedrone may be combined with heroin (Europol-EMCDDA 2010). Because of the capability of the drug to induce tolerance upon repeated doses, an increasing number of users reports have stated a quick progression to either regular drug use and/or uncontrolled bingeing behaviour (known as ‘fiending’), with 1-4 grams of mephedrone consumed in a session to prolong the duration of its effects (Deluca et al 2009; Europol-EMCDDA 2010). A recent survey carried out by a drug-related website has unveiled an average monthly use of 11.16 grams for each mephedrone consumer (Drugsforum 2010). Although withdrawal symptoms are not typically reported, users often describe strong cravings for the drug (Newcombe 2009). In a survey carried out in Scotland in February 2010, roughly 1 out of 6 users’ surveyed reported 'addiction

or dependence' symptoms associated with their mephedrone use (Dargan et al 2010).

Although one could argue about the limited generalizability of most studies here quoted and of the advice provided from online fora, according to web users mephedrone may be taken in combination with a number of stimulants, sedatives and psychedelics (Deluca et al 2009). These may include: cocaine; amphetamine; modafinil; butylone; MDPV; methylone; metamfepramone; alcohol; GBL/GHB; benzodiazepines; kratom (mytraginin); heroin; cannabis; ketamine (with this combination being known as ‘challenge’); MDMA; BZP; TFMPP; DMAA; and sildenafil. One could conclude that the above combinations are likely to increase mephedrone toxicity effects and harm potential.

DESIRED AND UNTOWARD MEPHEDRONE EFFECTS

Mephedrone effects have been variously compared by users to those of cocaine, amphetamine and MDMA. Self-reported subjective effects may include (Winstock et al 2010b; Deluca 2009):

- Intense stimulation and alertness, euphoria
- Empathy/feelings of closeness, sociability and talkativeness
- Intensification of sensory experiences
- Moderate sexual arousal
- Perceptual distortions (reported with higher dosages only)

According to Dargan et al (2010), some 56% of those who had used mephedrone may complain of at least one unwanted effect associated with its use; these may include (ACMD 2010; Deluca 2009; James et al, 2010; Wood et al 2009; Wood et al 2010b):

- *Gastrointestinal system:* Loss of appetite, dry mouth, nausea, vomiting and stomach discomfort
- *Central nervous system/neurological*: Tremors, tense jaws, trismus, bruxism, mild muscle clenching, stiff neck/shoulders, headache (very common), dizziness/light-headedness, tinnitus, seizures, nystagmus, pupil dilation, blurred vision, numbness of tactile sensitivity (reported at higher dosages)
- *Central nervous system/psychiatric*: Anxiety, agitation, confusion, dysphoria, irritability, aggression; depression, lack of motivation, anhedonia; time distortions, long-lasting hallucinations, paranoid delusions, short term psychosis, short term mania; insomnia and nightmares; impaired short term memory, poor concentration, mental fatigue. Psychopathological consequences are more frequently reported if the drug is taken at higher dosages/in prolonged sessions (Deluca 2009; Winstock et al 2010b) and/or if the misuser presents with an underlying psychobiological vulnerability (Odenwald et al 2005; Odenwald et al 2009).

- *Cardiovascular system*: Tachycardia, elevated blood pressure, respiratory difficulties, chest pain and elevated blood pressure, peripheral vasoconstriction. Possibly due to vasoconstriction, users have anecdotally described cold/blue fingers
- *Renal/urinary excretory system*: Difficulties in urination, possible nephrotoxicity, anorgasmia
- *Miscellaneous*: Changes in body temperature regulation, with hot flushes and sweating (so called ‘mephedrone sweat’, characterized by a strong body odour); painful nasal drip, nose and throat bleeds with burns and ulcerations (following insufflation); immunological toxicity (vasculitis, infections and ulcerations)

Most of the above untoward effects seem to be similar to those already documented for amphetamine, methamphetamine and MDMA (Schifano et al 2010), implicitly supporting a sympathomimetic activity of mephedrone. Conversely, symptoms of depression and anhedonia could be tentatively associated to a putative depletion of serotonin and dopamine as a consequence of drug use (ACMD 2010), similarly to what may occur with other stimulants (Schifano 1996). It is impossible to determine a ‘safe’ dose for mephedrone, since negative side effects may present in association with any dosage taken. Furthermore, similar dosages may have dramatically different consequences in different individuals (Dickson et al 2010).

TREATMENT and MANAGEMENT

Acute management of adverse events

The only available information relating to treatment of mephedrone acute behavioural toxicity derives from observations carried out in an Emergency Department in central London. In most cases, the mephedrone-related agitation was treated with benzodiazepines. All 15 patients were discharged after appropriate observation with no sequelae (Wood et al 2009; Wood et al 2010). Since no guidelines have yet been specifically provided, treatment is to be considered empirical. One could argue that the treatment for the more life-threatening conditions might be broadly similar to that of amphetamine poisoning. Those individuals presenting with less severe symptoms should be assessed and managed as for any other users of psychoactive drugs and may simply need reassurance, support and observation. People with underlying cardiac, neurological, and psychiatric conditions, especially those on medication, are likely to be at greatest risk of serious adverse events (Winstock et al, 2010a).

Longer term therapeutic psychological and harm reduction approaches

Harm reduction advice has been provided by pro drug websites, including using the drug not exceeding 500mg per session and dosing orally rather than insufflating (Newcombe 2009). Since too little is known about mephedrone potential neurotoxicity or long term consequences of its use, only commonsense advice about the use of any psychoactive stimulant has been provided (Winstock

et al 2010a). This may include: avoiding regular use to avoid developing tolerance; not using the drug in combination with other stimulants or large amounts of alcohol and other depressants; not injecting the drug; remaining well hydrated when using the drug; and avoiding becoming overheated. Both a brief motivational intervention and appropriately adapted psychosocial intervention have been suggested to treat mephedrone addiction (Winstock et al 2010a).

MEPHEDRONE RELATED DEATHS

During the last few months, British media and newspapers have been reporting about fatalities allegedly related to mephedrone consumption almost on a weekly basis, but only a proportion of them have already been confirmed. A report on a mephedrone-related fatality first appeared in Sweden, referring to an 18-years-old female death which occurred in December 2008. No other drugs, apart from mephedrone, were identified by the toxicological screenings (Gustaffson and Escher 2009). Previously, a Danish teenager found in possession of mephedrone died in May 2008, although toxicology reports were inconclusive (Campbell 2009). Published data regarding the first mephedrone-related death in the USA involved the combined use of mephedrone and heroin (Dickson et al 2010).

Data collected by the National Programme on Substance Abuse Deaths (Ghodse et al 2010) suggest that by the beginning of October 2010 there have been 45 suspected deaths related to mephedrone in England, 12 of in Scotland, 1 in

Wales, 1 in Northern Ireland and 1 in Guernsey. Preliminary analysis carried out in 48 out of these 60 cases has provided positive results for the presence of mephedrone at post mortem. Remaining cases are, to date, awaiting further investigation. It is important to emphasize that a number of fatalities reported to the np-SAD implicated mephedrone consumption in combination with other substances/other recreational drugs, such as alcohol, cannabis, cocaine, amphetamine, methadone, methylone and 4-MTA.

CONCLUSIONS

This paper may represent a comprehensive and critical review of the currently available information on the novel psychoactive drug 4-methylmethcathinone. Data have been collected from the very few published articles in scientific peer-reviewed journals, from official bodies' reports, and from the users' grey literature/pro drug websites. It is worth emphasizing the importance of the latter, since mephedrone was indeed first identified by the Psychonaut Web Mapping project (Deluca et al 2009) whilst examining new trends in drug use by actively monitoring drug users' orientated websites.

Although pharmacodynamics data are currently uncertain and further data from peer reviewed studies are needed, effects of 4-methylmethcathinone are reported to be broadly similar to those of MDMA/ecstasy and cocaine. In fact, mephedrone may feature mainly stimulant-like effects, such as mood enhancement and alertness, but possesses as well both empathogenic and

hallucinogenic properties at higher dosages. Only a few related case reports have been published so far, and there is a distinctive lack of information about the acute and chronic toxicity of 4-methylmethcathinone. In the UK, mephedrone has been tentatively associated with a number of deaths. However, most of them may have been reported by the popular press with some levels of inaccuracy, and this is likely to have generated confusion in the general public (Davey et al 2010). Preliminary data from the np-SAD here commented emphasize the need of continuing to monitor mephedrone. In fact, because of the recent appearance of the drug into the market, and the lack of mephedrone knowledge on the coroners' side, one could still think that the number of related fatalities has been under reported. It is worth noting that, after ban legislation came into effect, post-mortem samples taken in June 2010 in the UK have still tested positive for mephedrone (Ghodse et al 2010; Davies et al 2010).

A large quantity of personal advice and suggestions with respect to mephedrone dosage, best ways of experimenting with its effects and avoiding untoward reactions was here largely available in the websites we sampled. The technical knowledge on new products entering the market, hardly obtained through reference books and scientific journals, is often held in closed groups of users, who exchange online information with each other without any contact with the scientific world (Littlejohn et al 2005; Schifano et al 2006; Schmidt et al in press). Much of the material quoted here referring to web based sources was however not evidence-based and, for this reason, has proved to be difficult indeed to critically evaluate. In particular, we did not have any possibility to confirm if the

substance the misusers were referring to was indeed mephedrone. We did not survey here the actual *use* of the online information by interested web surfers, but only the availability and the content of data on mephedrone.

Future studies should better assess both the acute and chronic toxicity of mephedrone and related cathinone derivatives. With a better understanding of these drugs' clinical pharmacology, it is hopeful that related clinical management levels will improve. Furthermore, the characteristics of those consumers who take advantage of the online available information on mephedrone and similar compounds should be better assessed and, as a result, the stereotypical image of the 'drug misuser' may need to change (Littlejohn et al, 2005). Finally, the potential of innovative ICT prevention programmes for novel psychoactive compounds, such as the EC-funded 2010-2012 ReDNet research project (www.rednetproject.eu; Corazza et al in press) remains to be tested.

Mephedrone has been recently classified in both the UK and in a number of other countries as a measure to control its diffusion. One could argue that the designer drugs market appears to be constantly one step ahead of the authorities. Although it is beyond the scope of this paper to comment on the effectiveness of these control measures, it is a matter of fact that a few psychoactive compounds (e.g.: NRG-1; NRG-2; MDAi; MDPV etc) have recently entered the online market as substitutes for mephedrone. It is our opinion that only international collaborative efforts may be able to tackle the phenomenon of the regular offer of novel psychoactive drugs.

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Cathinone Mephedrone Amphetamine Phenethylamine

Figure 1. Mephedrone and related structures

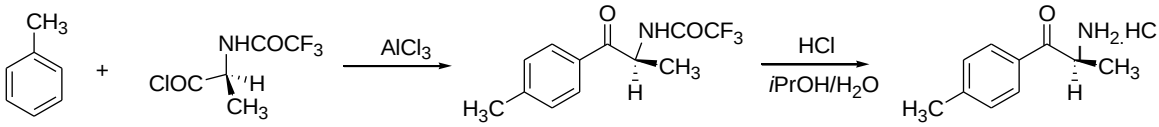

Figure 2. Stereoselective synthesis of (*S*)-4-methylcathinone

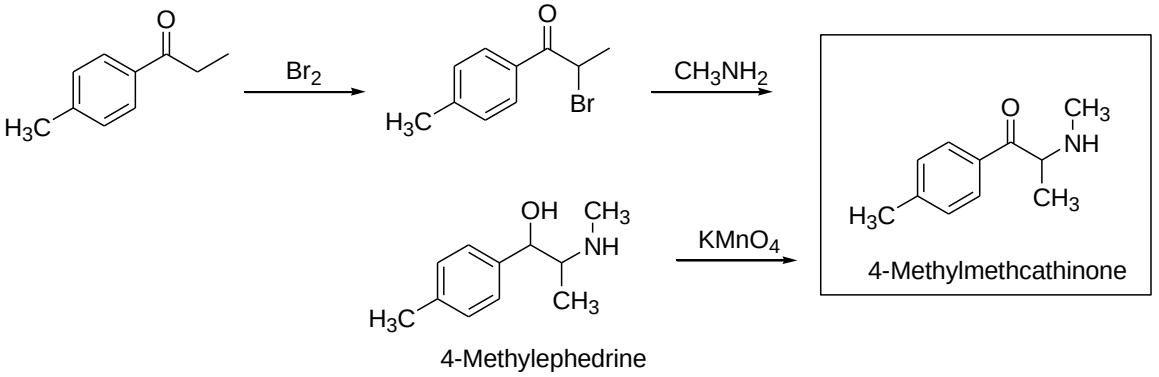

Figure 3. Synthesis of mephedrone