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Intended and Unintended Use of Cathinone Mixtures

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Keyword:	New psychoactive substances (NPS), Cathinones, Poly-NPS, NPS mixtures, Adulterants

Abstract

Introduction Cathinones are one of the most popular categories of new psychoactive substances (NPS) consumed. Cathinones have different pharmacological activities and receptor selectivity for monoamine transporters based on their chemical structures. They are incorporated into NPS mixtures and used with other NPS or 'traditional' drugs. Cathinone use represents significant health risks to individuals, and is a public health burden. **Methods** Evidence of poly-NPS use with cathinones, seizure information and literature analyses results on NPS mixtures was systematically gathered from online database sources, including Google Scholar, Scopus, Bluelight and Drugs-Forum. **Results and Discussion** Results highlight the prevalence of NPS with low purity, incorporation of cathinones into NPS mixtures since 2008, multiple members of the cathinone family being present in individual UK-seized samples. Cathinones were identified as adulterants in NPS marketed as being pure NPS, drugs of abuse, branded products, herbal blends and products labelled "not for human consumption". Toxicity resulting from cathinone mixtures is unpredictable since key attributes remain largely unknown. Symptoms of intoxication include neuro-psychological, psychiatric and metabolic symptoms. Proposed treatment includes holistic approaches involving psychosocial, psychiatric and pharmacological interventions. **Conclusion** Raising awareness of NPS, education and training of healthcare professionals is paramount in reducing harms related to cathinone use.

Key words: new psychoactive substances (NPS); cathinones; poly-NPS; NPS mixtures, adulterants

1. Background

In the past decade, the illicit drug market has expanded due to the emergence of a large number of new psychoactive substances (NPS). At the international level the focus is on new psychoactive substances which may pose a threat to public health. The United Nations (UN) defines NPS as: "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat" (UNODC, 2013a). The European Council uses a similar definition but extends the principle on the basis of comparable threats: "a new narcotic or psychotropic drug, in pure form or in preparation, that is not controlled by the United Nations drug conventions, but which may pose a public health threat comparable to that posed by substances listed in these conventions" (EMCDDA-Europol, 2012a). In the United Kingdom (UK), the Advisory Council on the Misuse of Drugs (ACMD) proposed a more pragmatic approach, referring to both the international conventions and the main UK drugs legislation incorporating them as well as slightly different purposes for consumption: "Psychoactive drugs which are not prohibited by the United Nations Single Convention on Narcotic Drugs or by the Misuse of Drugs Act 1971, and which people in the UK are seeking for intoxicant use" (ACMD, 2011).

The recent explosion of NPS on the market is thought to be due, in part, to information on synthesis of failed patents of pharmaceuticals with psychoactive effects becoming freely available over the internet (Karila et al., 2015). Increased accessibility to NPS via online markets, anonymity and discretion of online sale, lower prices compared to illicit narcotics and comparable desired effects and/ or improved activity from controlled drugs of abuse and their legal status in many countries have encouraged psychonauts and drug users to supplement their habit with NPS (EMCDDA, 2015). Unlike traditional drugs of abuse such as cocaine and MDMA (3,4-methylenedioxymethamphetamine or ecstasy), these drugs are often exceptionally complex to detect in the field and therefore provision of targeted clinical treatments to counteract toxicity and overdose is difficult.

The inherently complex nature of NPS with respect to their chemical heterogeneity, sustained emergence of new subcategories, high prevalence and limited available clinical expertise is contributing to significant public health threats. The patterns of abuse, multiple routes of administration, wide range of potency and actual content consumed often pose numerous unanswered questions upon admission to emergency rooms and mental health units (Schifano et al., 2015). Furthermore, suspected NPS can contain a pure substance or a mixture of substances, where the co-abuse of NPS with other drugs is usually unknown. Therefore, treatment decisions are often challenging and prediction of associated potential risks and harms is often not known until NPS-induced intoxication, poisoning, overdose and/ or fatalities are eventually reported. Stigma, self-treatment and lack of awareness of users are known factors which commonly lead to under-reporting and lack of knowledge on the size of the problem (Home Office, 2014a). In addition, due to the fast-moving nature of the NPS market, there is a limited availability of knowledge on the health implications and harms associated with the chronic use of NPS.

In light of the wide diversity of the newly emerging NPS and to enable their identification, in 2014, the United Nations Office on Drugs and Crime (UNODC) re-classified them into ten categories, with the most popular categories being cannabinoids, phenethylamines and cathinones (Levissianos, 2014). The popularity of both synthetic cathinones and cannabinoids was also confirmed in recent literature (Papaseit et al., 2014). Reported prevalence studies confirmed that cathinones are more prevalent than cannabinoids in specific populations e.g. among high-risk drug users (Bretteville-Jensen et al., 2013). Unlike cannabinoids, symptoms of intoxications resulting from cathinones are long-lasting, which may potentiate deaths (Fujita et al., 2016). This makes the study of cathinones mixtures an important aspect of NPS research in which there is still limited information with regards to their pharmacology, long-term and multi-drug use, unknown health consequences and toxicities (Nelson et al., 2014a; Zamengo et al., 2014).

1.1 Cathinones

Cathinones are synthetic analogues of the naturally occurring phenethylamine alkaloids present in khat trees (*Catha edulis*) (Hassan et al., 2006). Natural cathinones are amphetamine-like stimulants, but with lower potency than amphetamine (Patel, 2015). The main active components in khat are cathinone (S-(-)-2-amino-1-phenylpropan-1-one) and cathine (1S,2S-norpseudoephedrine). Natural cathinone is more abundant and potent than cathine. However, it is easily oxidised and transformed into cathine post-harvest (ACMD, 2013; Griffiths et al., 2010). The potency of khat fades after 36 – 48 hours as cathinone degrades to cathine, hence, the interest in synthetic cathinones which have a longer 'shelf-life' (Corkery, 2016).

1.1.1. Emergence of synthetic cathinones

In the 1990s, increased interest developed in the diverted use of first generation synthetic cathinones e.g. bupropion, methylone and pyrovalerone. Bupropion has low abuse potential with reported cocaine-cues in cocaine users (Vento et al., 2013). However, ephedrone has an increased abuse potential and has been shown to be more potent than cocaine and cathinone (Valente et al., 2014). Synthetic cathinones were initially abused in Australia, Canada, Mexico, China, Japan and some European countries including Finland, Germany, Hungary, Netherlands and Norway. This was followed by their emergence in the United States and Israel. Following their ban in Israel in 2008, cathinones appeared in greater numbers across 14 European countries (Valente et al., 2014). By 2009, the popularity of cathinones worldwide was greater than that of ketamine, phenethylamines, piperazines, plant-based substances or cannabinoids (UNODC, 2013b) and the public health risk posed by these substances became evident**.** The ban of the 'first generation' cathinones, in the UK, in 2010, led to the emergence of the 'second generation' cathinones often referred to as 'NRG'. NRG products included naphyrone, a 'legal' cathinone at the time. Analysis of NRG products purchased over the internet showed the inclusion of 'illegal' cathinones such as mephedrone, flephedrone, butylone, pentylone, 4-methylethcathinone and MDPV (3,4-methylenedioxypyrovalerone) (Valente et al., 2014). Despite attempts to legislate against them, the popularity of cathinones continued to increase. By 2011, the use of cathinones in Brazil, Greece, Luxembourg, Moldova, Mongolia, Singapore and Turkey was being reported (UNODC, 2013a) and in 2010 and 2011, synthetic cathinones along with synthetic cannabinoids, were reported as the most consumed types of NPS around the world (Newcombe, 2013). The popularity of cathinone use was highest in Europe in 2012 (UNODC, 2013b). Between 2008 and 2015, a survey of over 95 countries showed that cathinones ranked third, after cannabinoids and phenethylamines, in terms of total number of the most-widely abused categories of NPS; mephedrone was the most prevalent cathinone in terms of popularity and hospital presentations (EMCDDA, 2016a; Karila et al., 2015; UNODC, 2015a). The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)'s latest report shows that of the 98 NPS notified during 2015, 26 were cathinones and 24 synthetic cannabinoids; these together with phenethylamines account for the largest number of NPS (EMCDDA, 2016d). By the end of 2016 the number of NPS notified to the EMCDDA's European information system and database on new drugs (EDND) since 2005 was 629. Of these, 171 were synthetic cannabinoids, 118 were synthetic cathinones. In 2016, 10 new cannabinoids and 14 new cathinones were reported (EMCDDA-EDND, 2017).

1.1.2. Popularity and prevalence of cathinones

Wide diffusion and popularity of synthetic cathinones compared to commonly abused drugs is thought to have been influenced by economic, social and psychoactive determinants. Users reported that they were good value for money, with fewer side-effects due to short duration of action and a 'better high' than cocaine, MDMA and amphetamines, and they were easily obtained, which was perceived as a bonus. Cathinones are not only used recreationally but have also been abused in sports, probably due to their intense stimulant effect (Mazzoni et al., 2014). Drug users have reported that a cathinone-induced stimulant effect was comparable to methylphenidate at low doses or to a combined effect of both amphetamine and cocaine at high doses (Coppola & Mondola, 2012a). Users consider cathinones to be equipotent and pharmacologically similar to cocaine, amphetamine and MDMA (EMCDDA-

Europol, 2012a). In addition, cathinones were, at the time, 'legal' and hence assumed to be 'safe'. This meant they did not have the social stigma for users associated with the abuse of illegal drugs. In 2009, the popularity of mephedrone or 'bubble' in the UK soared (Measham et al., 2011), but the reason for this is not well understood. Users' interviews and surveys postulated that increased popularity and convenience of purchasing mephedrone was linked to the unavailability, high price and impurity of several common illicit drugs, especially stimulants such as amphetamine, cocaine and MDMA (ACMD, 2010; Carhart-Harris et al., 2011; Measham et al., 2010). Although it was originally thought that the rapid growth in interest and use of synthetic cathinones, especially mephedrone, notified at the end of 2000s, was in part due to the large decrease in purity of ecstasy and cocaine, and instability of the ecstasy market, as mentioned above, recent studies indicated that instead of replacing or displacing ecstasy and cocaine, mephedrone, and most likely other NPS from this group, appeared to have been added to the established repertoires of psychostimulant narcotics (Schifano et al., 2016b).

Following its control in the UK in April 2010, the reported use of mephedrone did decline but it has not disappeared (Lader, 2016; NACDA & DHNI, 2016; Black et al., 2016; Ipsos-MORI, 2015). If anything, it has now become part of the drug repertoire provided by illicit drug dealers (Shapiro & Daly, 2017) and consumed by users alongside other stimulants. Although now controlled together with MDPV and methylone under schedule 2 of the United Nations Convention on Psychotropic Substances 1971 (UNODC, 2015b), and technically no longer an NPS, mephedrone still requires monitoring and investigating, especially since mephedrone-related dependence and fatalities continue to occur on a regular basis (PHE, 2017; ISD, 2016; ONS, 2016; NRS, 2016; NISRA, 2016). Synthetic cathinones have been widely prevalent among clubbers, high-risk drug users such as heroin-injecting users, MSM (i.e. men who have sex with men) and abstinence treatment entrants (EMCDDA, 2015; Heikman et al., 2016). 'Slamming' (i.e. intravenous administration) cathinones became very popular in group sex because it improves mood and induces sexual disinhibition (Batisse et al., 2016). Unsafe practices related to injecting cathinones (10 – 20 times/ day) have become very popular among illicit drug users, ex-opiate users, MSM and prisoners (EMCDDA, 2015; Schifano et al., 2016b; Wagner et al., 2014).

1.2. Emergence of NPS mixtures

Unlike pharmaceuticals, NPS are commonly produced in clandestine laboratories and hence are not routinely produced or controlled according to 'Good Manufacturing Practices' (GMP) (Chintalova-Dallas et al., 2009). With the reduced availability of drugs of abuse e.g. MDMA (see above) purity declined and illicit drugs were cut to maintain their weight and enhance dealers' profits (Brunt et al., 2011). New psychoactive substances have also been shown to be produced as mixtures to enhance their effect to mimic the effects of popular illicit drugs (EMCDDA-Europol, 2012b). Compounds sold as pure substances often contained mixtures of one or more controlled, as well as uncontrolled, active substances.

New psychoactive substances seized between January 2011 and March 2012 contained mixtures of up to eight different controlled or uncontrolled NPS or cutting agents (Home Office, 2015). Mephedrone samples collected in south Wales over the period November 2011 to March 2013 showed that mephedrone percentage mean purity was 68 ± 25 % (Miserez et al., 2014). In 2013, the UK Forensic Early Warning System (FEWS) reported that 81 % of seized NPS contained mixtures including more than one active ingredient. Of those, 36 % included two different active ingredients, 35 % included three different active ingredients and 1 % of samples contained seven different active ingredients (Home Office, 2013). In 2014, the number of seized NPS substances containing mixtures increased to 91 %, as reported by FEWS. Of those, 61 % included two different active ingredients and 30 % included three different active ingredients (Home Office, 2014b). In 2015, the use of mixtures was still prevalent in 55 % of seized samples seized (Home Office, 2015). This demonstrates that NPS used are often cut or mixed with other substances. Information is still lacking on the current trends for mixtures of cathinones. To our knowledge, currently no statistical data are publicly available regarding the prevalence of cathinone mixtures.

Intentional or unintentional interplay between NPS and traditional drugs of abuse (EMCDDA, 2016c; UNODC, 2015a), mix-and-matching of NPS with psychoactive and non-psychoactive substances, via mixture intake or sequential consumption of numerous substances, with or without alcohol, has the potential to induce multiple drug intoxication and/ or fatalities. There is limited knowledge on this aspect in the NPS area, which we aim to explore in this article through cathinone mixtures, presented as an example of a popular NPS class. The rationale of this paper is to review current trends in mixing or co-abusing synthetic cathinones with other psychoactive or non-psychoactive substances, as well as review the potential risks and harms resulting from the intake of these mixtures.

2. Methods

Evidence of poly-NPS use including cathinones, seizure information and literature analyses results on NPS mixtures was systematically gathered from database searches. Due to the limited published work in this area, potential multi-intoxications and societal harms associated with the intake of cathinone mixtures, databases were searched for all papers, government and user reports related to cathinones. A literature search was systematically conducted using scientific databases such as Google Scholar and Scopus and popular drug fora such as Bluelight and Drugs-Forum. No information was available from publicly available pages on Erowid drug fora. The following search terms were used: 'cathinones', 'cathinone mixtures', 'poly-drug and new psychoactive substances', 'poly-drug and cathinones', 'cathinone combo', 'bath salts', and 'NPS injections'. Information was sought for the period 2009, when cathinones first emerged in the UK, to the present. Information was also gathered from official and government reports such as ACMD, EMCDDA, UNODC, FEWS and policy papers as well as confidential seizure reports. Information extracted included data on substances found in the adulteration of cathinone products, popular substances co-abused with cathinones and information related to the implications of multi-substance use including cathinones.

3. Results and Discussion

This following section highlights the problem of intentional or unintentional use of multiple NPS mixtures containing cathinones simultaneously or sequentially and the potential risks and harms that may be associated with these unsafe practices. The prevalence of cathinone product adulteration with other NPS, drugs of abuse, active adulterants or cutting agents is also presented.

Search results on Scopus identified 921 papers, whereas the searches via Google Scholar identified 3000+ papers (2013 – 2016). For this article, 200 papers were identified as relevant. Less than 10 results were identified from the above-mentioned drug fora.

3.1. Simultaneous use of NPS mixtures containing cathinones

3.1.1. Cathinone mixtures identified

The rapid emergence of uncontrolled, untested, impure NPS compounds constitutes a major public health risk (Karila et al., 2015). The purity of NPS has been shown to decline over time; a trend observed in particular for the cathinone class of NPS. For example, the 'Psychonaut' web mapping research group identified 140 cathinone products sold as mixtures out of 414 products reported from 203 websites during the period January 2008 to December 2009 (Deluca et al., 2012). The analysis of seized MDPV products showed that purity decreased from 100 to < 10 % over approximately three years (October 2008 to June 2011) (Zuba & Byrska, 2013a). Furthermore, varied adulteration of cathinones became more prevalent. From October 2008 to June 2011, the analysis of 445 powders of NPS seized from headshops in Poland showed that 45 % of the products contained cathinone (77.6 % purity) and piperazine (56.1 % purity) mixtures mostly adulterated with 2C-B (2,5-dimethoxy-4-bromophenethylamine), 2C-E (2,5-dimethoxy-4-ethylphenethylamine), 2- and 4-aminoindanes, 4-FA (4-fluoroamphetamine), 4-OH-MET (4-hydroxy-N-methyl-N-ethyltryptamine), 5-HTP (5-hydroxytryptophan), benzocaine, caffeine, dimethocaine, DOET (2,5-dimethoxy-4-

ethylamphetamine), DMAA (3,4-dimethoxy-N-methylamphetamine), fenfluramine, lidocaine, pFBT (4-fluorotropacocaine), procaine, metoclopramide, mexiletine, tadalafil and theobromine (Zuba & Byrska, 2013a). Of those, 105 (23.4 %) contained a mixture of two constituents, 55 (12.2 %) of three, 26 (5.8 %) of four and 16 of more than four constituents in the mixture (Zuba & Byrska, 2013a). Mephedrone samples purchased in south Wales, cut with creatine, monosodium glutamate and sucrose were 33 % pure (Miserez et al., 2014). Some mephedrone samples in the same study were cut with 4-FMC (4-fluoromethcathinone) and 4-MEC (Miserez et al., 2014). In Poland, two-thirds of buphedrone samples seized by a law-enforcement raid in 2010 were found to contain 4-MEC (methylethcathinone) and MDPV (Zuba et al., 2013b). In a large study investigating 60 NPS purchased over the internet during 2012 – 2013, a product sold as APB ((2-aminopropyl) benzofuran) was found to contain 5-APB (5-(2-aminopropyl) benzofuran) and pyrovalerone (Guirguis et al., 2017).

In 2015, confidential reports on UK NPS cathinone samples submitted for forensic analysis included both single and multiple cathinones as well as other NPS such as ephedrine, ethylphenidate, ketamine, MDMA and methamphetamine (Daily, 2016). In its 2016 risk assessment report, the EMCDDA reported that seized products containing α-PVP (α- pyrrolidinopentiophenone) also contained other NPS including additional cathinones such as MEC (methylethcathinone), MMC (methylmethcathinone), pentedrone, MDPBP (3',4'-methylenedioxy-α-pyrrolidinobutyrophenone), ethylcathinone and MDPV; synthetic cannabinoids; MPA (methylthienylpropamine); tryptamines such as 5-MeO-MiPT (5-MeO-N-Me-N-isopropyltryptamine) and AMT (α-Me-tryptamine); 2-DPMP (2-(diphenylmethyl)piperidine)); arylcyclohexamines such as ketamine and methoxetamine (MXE); MMA (*p*-MeO-methamphetamine); benzodiazepines such as etizolam and flubromazolam; traditional drugs of abuse such as MDMA, cocaine, amphetamine and heroin; and common cutting agents and/or active adulterants such as benzocaine, lidocaine and caffeine (EMCDDA, 2016c). Information gathered by EMCDDA-EUROPOL revealed that seized MDPV samples were mainly mixed with other cathinones; adulterants such as phenethylamines, cannabinoids and piperazines; and cutting agents such as benzocaine, caffeine and lidocaine (EMCDDA-Europol, 2014). Furthermore, popular cutting agents such as calcium carbonate, taurine and creatine were found in cathinone samples seized in the UK (Stewart et al., 2012). Cutting agents used in research studies involving cathinones included sucrose, glucose, lactose and mannitol (Khreit et al., 2012). Adulterants such as caffeine, lidocaine, procaine and benzocaine were found in NRG samples purchased over the internet (Brandt et al., 2011; Brandt et al., 2010). Up to 2010, the ACMD reported that both controlled drugs of abuse and NPS substances such as amphetamine, benzylpiperazines, cocaine and ketamine were co-added as adulterants to cathinone products (ACMD, 2010).

In general, and in a similar manner to illicit drugs (Cole et al., 2010), NPS may be formulated into products by being mixed with cutting and bulking agents and fillers, which may have been purposely added. Some adulterants and bulking agents such as benzocaine, caffeine, lidocaine, phenacetin and procaine are generally added in combination with NPS and with cathinones in particular (Alotaibi et al., 2015; Kavanagh et al., 2012) because they may mimic, enhance and potentiate the effects of controlled drugs of abuse (Zuba & Byrska, 2013a). From 2012 to 2016, sucrose, glucose, lactose, mannitol, monosodium glutamate and taurine were common cutting agents associated with UK cathinones-seizures, creatine and monosodium glutamate being the most popular (Daily, 2016). Both monosodium glutamate and taurine are known food supplements, whereas sucrose gives a sweet taste. Adulterants such as 2- and 4-aminoindane, and fenfluramine may enhance the stimulant effect of cathinones, whereas DMAA may exert benzylpiperazine and MDMA-like effects (Zuba & Byrska, 2013a). Lidocaine is a local anaesthetic and may be incorporated in NPS mixtures for its numbing effect, whereas both benzocaine and procaine have been shown to be used as adulterants for their cocaine-like effect (Zuba & Byrska, 2013a).

Adulterants and cutting agents, which may be co-added or co-ingested with NPS substances in general to counteract their side-effects, include calcium carbonate, diltiazem, hydroxizine, metoclopramide, paracetamol and phenacetin (Coppola & Mondola, 2012a; Zuba & Byrska, 2013a). For example, benzodiazepines were found to be co-ingested with MDPV to counteract its excitatory effect

(EMCDDA–Europol, 2014). In cathinone samples, calcium carbonate may be incorporated to counteract stomach acidity, whereas hydroxyzine may be incorporated for its sedative effect (Coppola & Mondola, 2012a). Diltiazem is a rate-limiting anti-anginal drug and is potentially co-added to these mixtures to counteract the cardio-stimulant effect induced by stimulants. Arguably, however, diltiazem may be added to drug preparations to 'modulate' the stimulant, including synthetic cathinones, behavioural responses (Mills et al., 2007). Metoclopramide is a prokinetic anti-emetic, which is possibly co-added/ co-ingested to counteract nausea and vomiting side-effects. The inadvertent incorporation of this adulterant may also add public health risks. For example, metoclopramide may induce extrapyramidal symptoms in young adults, whereas diltiazem is contraindicated in pregnancy (eMC, 2016a, 2016b).

Adulterants and cutting agents may have similar chemical structures to target drugs in order to add to the complexity of the mixture (Noonan et al., 2009; Ryder, 2002; Ryder et al., 2000) and may have a stronger/ masking detection signal that the target NPS and, hence, may hinder identification (Assi et al., 2015; Guirguis et al., 2017). Typical examples includes the similarity in the chemical structures of nicotinamide and cathinone, stronger detection signal of benzocaine (Guirguis et al., 2017), or masking signal of impurities (e.g. dyes or cutting agents such as microcrystalline cellulose) (Assi et al., 2015; Guirguis et al., 2017). In 2014, adulterants over which UK law enforcement agencies have gained power to seize if they suspect that they are used for cutting NPS included lidocaine, benzocaine and phenacetin (Home Office, 2014c).

3.1.2. Mislabelled cathinone mixtures

New psychoactive substances are often mislabelled and do not contain what the label claims. Synthetic cathinones have been shown to be incorporated in controlled drug mixtures as adulterants. A Spanish project carried out the identification of drugs of abuse from 2009 until 2012. 2-MMC (2-methylmethcathinone) was found to be incorporated in MDMA tablets; 4-MEC in both MDMA powder and ketamine; buphedrone and butylone in cocaine; mephedrone in MDMA tablets, MDMA powder, amphetamine and ketamine; and methylone in MDMA tablets and powder (Giné et al., 2014). In 2009, the Dutch Drug Information and Monitoring System (DIMS) reported that variable amounts (96 – 150 mg/ tablet) of mephedrone were covertly included in tablets sold as MDMA (Dargan et al., 2011). Recently, the analysis of illicit samples revealed that they contained α-PBT (alpha-pyrrolidinobutiothiophenone) and α-PVP and their bromothienyl analogues (Doi et al., 2016).

In addition, NPS are often deliberately branded to imply legality and safe use. However, they may include a mixture of NPS with cutting agents, active adulterants (Zancajo et al., 2014) or reaction by-products (Chintalova-Dallas et al., 2009; Varlibas et al., 2009). In 2009, Parkinsonism was induced following the intake of a Russian cocktail 'Boltushka' of methcathinone found in Odessa (Ukraine). It was postulated that this may have resulted from potassium permanganate impurities remaining from the synthesis of the home-made methcathinone (Chintalova-Dallas et al., 2009; Varlibas et al., 2009). Similarly, in Estonia, the intake of methcathinone and high levels of potassium permanganate using 'kitchen chemistry' have been shown to induce irreversible progressive neurological damage (Sikk & Taba, 2015). This shows the potential harm which may arise from the inadvertent consumption of unstated ingredients. Cathinone mixtures distributed as 'bath salts' have been shown to contain cathinones and piperazines (Davies et al., 2010; German et al., 2013), caffeine (Baumann et al., 2013a) or methylone, MDPV and mephedrone (Gershman & Fass, 2012). Gershman and Fass (2012) have emphasised that 'bath salts' products found in the US mainly contain cathinone analogues i.e., mephedrone, methylone and MDPV and may also contain local anaesthetic such as lidocaine (Gershman & Fass, 2012; Schneir et al., 2014). The content of some brands have been shown to change over time because of legislation. The same brand may not contain the same NPS over time (Van Buskirk et al., 2013; Zuba & Byrska, 2013a). 'Bath salts' have been shown to be adulterated with 1-benzylpiperazine, amphetamine, benzocaine, caffeine, cocaine, ketamine, lidocaine, opiates and paracetamol (Cottencin et al., 2014; McGraw & McGraw, 2012; Watterson et al., 2012; Zawilska & Wojcieszak, 2013). Two products, branded as 'Cotton cloud' and 'Energising aromatherapy powder', were purchased by researchers from the US. They were labelled as 'bath salts' and

'potpourri', respectively. Chemical analysis revealed that the former contained three cathinones: mephedrone, methylone and MDPV, whereas the latter contained MDPV and caffeine (Spiller et al., 2011).

Brandt et al. (2010) reported the detection of cathinone mixtures in internet samples misleadingly labelled NRG-1 and NRG-2 Undeclared mixtures found in NPS products purchased from the internet included: 3-FMC (3-fluoromethcathinone) and caffeine; ethcathinone, mephedrone and caffeine; ethcathinone and mephedrone (Davies et al., 2010). Three packages were found in a car involved in a car accident, resulting in the death of the driver. The packages were labelled as 'ivory speed' and 'exclusive dust' with inscriptions 'collector's product for field stone rinsing' and were shown to contain mixtures of buphedrone and MDPV (Zuba et al., 2013b). Furthermore, the analysis of mephedrone street samples showed that one capsule marketed by 'neorganics', branded as 'sub coca 2' contained α-phtalidomipriophenone and 2-fluoromethamphetamine. Other capsules branded as 'neodove' and 'sub coca' contained mephedrone, caffeine, N-ethylcathinone and α-phtalidomipriophenone (Camilleri et al., 2010). Table 1 shows examples of branded NPS products and the actual content identified. These examples show that branded NPS products contained cathinone mixtures and cathinones mixed with other NPS substances, adulterants and cutting agents. The maximum number of NPS substances included in these branded NPS products was five.

< Table 1 about here >

The analysis of 14 NPS street samples showed that the amounts of active ingredients ranged from 11 to 73 %. A sample branded as 'recharge' was found to contain 42 % mephedrone, whereas another sample branded as 'ocean burst' was found to contain 38 % total active compounds including ethcathinone, 4-MEC and butylone (Leffler et al., 2014).

In its joint report on MDPV, the EMCDDA-EUROPOL revealed that MDPV products seized in Germany from February 2011 to November 2013 involved branded products such as 'Mojo', 'Mitseez', 'Buzz Powder', 'Sweed', 'Ivory Wave', 'J White Powder Cleaner', 'wakup', 'Yellow Submarine', 'XXX', 'Buty', 'Lionheart', 'Rush Hour', 'Lets play crack inside', 'Charlie Sheen', 'All Day, All Night –What the fuck', 'Highway', 'ECKO', 'Brutal Powder', 'Sextacy', 'Insomnia' and 'Ultra Charge'. In these products, MDPV was mainly mixed with 4-MEC, flephedrone, butylone, MDPBP (3',4'-methylenedioxy-α-pyrrolidinobutyrophenone), TFMPP (3-trifluoromethylphenylpiperazine), 3-FMC, MXE, 2C-E, *p*-fluoramphetamine, AM-2201 ((1-(5-fluoropentyl)-3-(1-naphthoyl)indole)), pentedrone and/or benzocaine, caffeine, lidocaine, mannitol, starch and taurine (EMCDDA–Europol, 2014).

NPS products advertised as herbal blends have also been shown to contain cathinone mixtures. The narcotic department in Istanbul published reports on the analysis of herbal samples obtained between August 2010 and March 2012. The analysis showed that some samples included mixtures of mephedrone and MDPV; cathinones and cathine, respectively (Gurdal et al., 2013). NPS products advertised as 'not for human consumption' have been shown to contain cathinone mixtures. A product labelled as 'mosquito repellent' was found to contain MDPV and the cannabinoid JWH-018 ((1-pentyl-3-(1-naphthoyl)indole)) (Adamowicz et al., 2013). Branded products labelled as 'plant feeders', 'bath salts' or 'plant food' have also been shown to contain cathinone mixtures (Table 1) (Araújo et al., 2014; Leffler et al., 2014).

Inconsistencies in the composition of identical NPS brands and the reduced/ variable purity pose unpredictable public health risks and highlight the challenges faced by front-line and law enforcement agents. This is because of the unknown drug-drug interactions, drug-morbidity interactions and unpredictable idiosyncratic effects, which may result in multiple-drug intoxications. Heterogeneity of NPS products pose notable challenges for the police and forensic laboratories in terms of time and financial costs involved, selection of representative samples for forensic statistical analysis, which highlights the existing need for efficient on-site screening, detection, identification and analysis (UNODC, 2009; Zuba & Byrska, 2013a).

3.2. Poly-substance use involving cathinones

Poly-substance use is posing a global public health risk due to unknown modes of action of individual NPS, unexpected multiple intoxications and inability to identify the causative substance(s) (Aromatario et al., 2012; Council of Europe, 2012; Herzig et al., 2013; INCSR, 2013). Users favour unpredictable effects of poly-drug use and seek maximum mind alteration and disinhibition, known as "the garbage head syndrome" (Iudici et al., 2015). Poly-substance use has also been practised by drug users in order to counteract the side-effects or prolong the effect(s) of a drug of abuse or to replace a non-available, expensive illicit drug or low-purity drugs (as above) (Clayton, 1986). For instance, a study found that arrested drivers used MDPV to get effects that mimic those of amphetamine (Ojanperä et al., 2011). Over a period of one year, from autumn 2009, a study found that 259 cases of arrested drivers in Finland tested positive for MDPV. Of those, 80 % used MDPV with amphetamine, 67 % co-ingested benzodiazepines, whereas only 8.5 % had used alcohol (Kriikku et al., 2011). Multiple NPS, illicit drugs and/ or alcohol were detected in blood and urine of 84 % (170 cases) of 203 in life or post-mortem cases. The most common NPS identified included mephedrone and 4-MEC. Other cathinones identified included 4F-MEC, MDPV, methylone, butylone, pentylone, pentedrone and naphyrone. Examples of co-ingested substances include: "alcohol (77 cases), antidepressants (50), cocaine (47), amphetamines (44), opioids (43), benzodiazepines (38), cannabis (36), cocaine adulterants (35), paracetamol (14), antipsychotics (12), ketamine (11), ibuprofen (9), quinine (6), sildenafil (5), ephedrine (5), antihistamines (4), carbon monoxide (3), anticonvulsants (3), cardiac drugs (3), gastric drugs (3), zopiclone (2), chloroquine (1), GHB (γ-hydroxybutyrate) (1) and trimethoprim (1)" (Elliott & Evans, 2014).

McCabe et al. (2006) reported that poly-substance use usually followed sessions of bingeing alcohol. Sessions involved the use of more than four classes of drugs including 'stimulants (uppers)' and 'depressants (downers)'. Combining alcohol and mephedrone is very common (Ciudad-Roberts et al., 2016). O'Neill & McElrath (2012) reported the preference of alcohol bingeing before the ingestion of mephedrone by party-goers, whereas 'sippers' preferred sipping alcohol while ingesting mephedrone. In contrast, 'remedy-makers' preferred using alcohol following the ingestion of mephedrone to reverse its side-effects.

Poly-substance consumption in a single session is very widely discussed in online drug fora and has been reported in post-mortem case reports (Cosbey et al., 2013; Marinetti & Antonides, 2013). Discussions on drug fora (Bluelight, 2012) revealed that NPS are co-ingested with numerous drugs of abuse from the known repertoire. In 2010, a survey undertaken in two South London gay dance clubs was able to capture data from 207 clubbers. Of those, 46 and 41 % mixed or intended to use mephedrone with MDMA and cocaine, respectively (Measham et al., 2011). Post-mortem inquests showed that deceased cases have co-ingested up to eight different classes of drugs, up to ten drugs in a session (Marinetti & Antonides, 2013). The *Lancet* has reported poly-substance use in gay and lesbians club and sex 'chill-outs' parties. Drugs often consumed during partying included MDMA, mephedrone, cocaine, GBL (γ-butyrolactone) and ketamine (Kirby & Thornber-Dunwell, 2013), whereas drugs preferred in 'chemsex' sessions included MDMA, mephedrone, GBL and methamphetamine (Bourne et al., 2015).

Furthermore, the EMCDDA (2010) has reported that mephedrone was occasionally co-abused with alcohol or controlled drugs such as heroin (EMCDDA-Europol, 2010), cocaine, cannabis, ketamine and MDMA (ACMD, 2010), either to enhance the pharmacological effects or attenuate the wearing-off effect (Newcombe, 2009). It was also reported that mephedrone was co-abused in conjunction with other cathinones such as methylone, MDPV, butylone; other NPS such as GBL, kratom (*Mitragyna speciosa*) and other prescription medicines such as benzodiazepines (Deluca et al., 2009). van Hout (2014) documented reports from drug fora regarding the intention of 4-MEC users to consume it with 3-MMC (3-methylmethcathinone), MPA (methiopropamine), 5,6-MDAI (5,6-methylenedioxy-2-aminoindane), flephedrone, methylone, butylone, 2-FMA (2-fluoromethamphetamine), PV8 (α-pyrrolidinopentiophenone) MDPV substitute, 4-BMC (4-

bromomethcathinone), 4-EMC (4-ethylmethcathinone), pentylone, NEB (N-ethylbuphedrone), 2C-E (4-ethyl-2,5-dimethoxyphenethylamine), 4-FMA (4-fluoromethamphetamine), 4-FA, 4-FMP (4-fluoromethamphetamine), MXE and pentedrone (van Hout, 2014). The logistic regression analysis of reported data by synthetic cannabinoids and synthetic cathinone users revealed that synthetic cathinones are mostly co-ingested with methamphetamine and club drugs, i.e. ketamine and MDMA (Wagner et al., 2014).

Limited information was available from Bluelight and Drugs-Forum on preferred cathinone combinations. Users reported the intake of mephedrone and heroin, also known as a 'speedball' combo (Karila et al., 2015). Experiences shared over the period between 2010 and 2015 included the intake of mephedrone with Viagra (Cialis) to boost libido, and the intake of 4-MEC with 'weed' and GBL during 'chemsex' sessions (Drugs-Forum, 2010a, 2010b, 2015). In contrast, a user shared his experience with a methylone, 4-FA and MDA (3,4-methylenedioxeamphetamine) combo and reported suffering from neck and head twitching lasting for two months, an adverse effect that re-occurred upon subsequent intake of 4-FA (Bluelight, 2011, 2012). Furthermore, numerous MDPV combinations were reported. For example, combinations of MDPV with cocaine; amphetamines and methamphetamine due to their entactogenic effects; combinations with cannabis; kratom; other cathinones; alcohol; β-blockers such as propranolol to counteract tachycardia; GBL, GHB and 5-MeO-MiPT (5-methoxy-N-methyl-N-isopropyltryptamine) to improve libido; zopiclone to enhance visual hallucinations; caffeine for its stimulant effect; famotidine, omeprazole and domperidone to counteract stomach pain; pregabalin; opiates; and benzodiazepines for their anxiolytic effect (Coppola & Mondola, 2012b; Katz et al., 2014). A case study by Bertol et al. (2014) reported a patient, presenting at an ED with multiple drug intoxication, was taking/ injecting the cathinones MDPV and/ or pentedrone and/ or 3-MMC. The patient was also taking pregabalin, alprazolam, aripiprazole and fluoxetine on prescription. Urine analysis showed additional metabolites for chlordiazepoxide, diazepam and temazepam, which the patient was taking to help him with insomnia. Intoxications could not be assigned to an individual drug or multiple drugs, showing the challenge at the point of treatment decision-making (Bertol et al., 2014).

3.3. Pharmacology related to the (poly)-intake of cathinone mixtures

The only cathinones under international control (United Nations Convention on Psychotropic Substances 1971) are amfepramone, cathine, cathinone, mephedrone, methcathinone, and pyrovalerone. Although mephedrone (4-methylmethcathinone) was originally synthesized in 1929, it first appeared on the drug scene in 2008 (Schifano et al., 2011), and synthetic cathinones currently account for the second largest group of substances monitored by the EMCDDA (2016b). Of the hundred or so cathinones notified to date to the EMCDDA, those which are of particular concern are mephedrone, 4-MEC, α-PVP, flephedrone, 3′,4′-Methylenedioxy-α-pyrrolidinobutyrophenone (MDPBP), MDPV, methedrone, methylone, naphyrone, pentedrone and pyrovalerone.

Limited information is available on the pharmacology and toxicology of cathinones (Green et al., 2014; Schifano et al., 2016a; Valente et al., 2014). Cathinone analogues exhibit various pharmacological effects including stimulant (increasing alertness, euphoria), empathogenic (increased empathy) and anti-depressant (improving mood) effects (ACMD, 2010; Erowid, 2013). Coppola and Mondola (2012a) and Cozzi et al. (1999) showed that cathinones may exert their stimulant effect by inhibiting the enzymes tyrosine hydroxylase and tryptophan hydroxylase, which are responsible for the synthesis of DA and 5-HT (Coppola & Mondola, 2012a; Cozzi et al., 1999). Cathinones also inhibit the re-uptake of the neurotransmitters DA, 5-HT and norepinephrine (NE) by the monoamine transporters, from the synaptic cleft, which results in reduced clearance of neurotransmitters from the cleft. Additionally, they induce the release of newly synthesised monoamines from both the cytoplasm as well as stored monoamines from the synaptic vesicle stores. These pharmacological effects result in reduced concentrations of monoamines in the frontal cortex, hippocampus and neostriatum (Gygi et al., 1996; Gygi et al., 1997; Sparago et al., 1996). Cathinones target the monoamine transporters serotonin, dopamine and norepinephrine transporters (SERT, DAT and NET, respectively) and the

nicotinic anticholinergic receptors (e.g. bupropion), in a similar manner to traditional drugs of abuse (Baumann et al., 2011; Simmler et al., 2013a).

Despite that, many of the newly emerging cathinones are amphetamine derivatives, chemical substitutions on the amphetamine 'core structure' alter potency at the NET, DAT, and SERT transporters (Baumann et al., 2012; Cozzi et al., 2013; Eshleman et al., 2013; Iversen et al., 2013; Simmler et al., 2013a, 2014a, 2014b). Therefore, cathinones have been classified based on their pharmacological action (i.e. DAT/SERT inhibition ratio) and comparability to traditional drugs of abuse; in particular:

1) Cocaine-MDMA-mixed cathinones, e.g. mephedrone, 4-MEC, methylone, etylone, butylone and naphyrone. These are substrates for the DAT, SERT, and NET. These molecules are associated with an entactogenic, MDMA-like, effect when ingested orally, and with a psychostimulant cocaine-like effect when being administered intranasally (Liechti, 2015);

2) Methamphetamine-like cathinones, e.g. cathinone, methcathinone, flephedrone, ethcathinone and 3-fluoromethcathinone. These are monoamine transporter substrates with DAT selective profiles, exhibiting high inhibitory potencies at DAT and lower inhibitory potencies at SERT (Simmler et al., 2013b and 2014a). They also induce both DA and NE release similar to methamphetamine (Liechti, 2015);

3) MDMA-like cathinones, e.g. methedrone and 4-trifluoromethylmethcathinone. These molecules exhibit a greater inhibitory potency at SERT as compared to their inhibition to DAT, whilst inducing the release of both NE and 5-HT similar to amphetamine analogues such as paramethoxymethamphetamine (PMMA), paramethoxyamphetamine (PMA), 4-ethylthioamphetamine (4-MTA); and MDMA (Simmler et al., 2014a).

4) Pyrovalerone-cathinones: e.g. pyrovalerone, MDPV and α-PVP. These molecules are non-substrate transporter inhibitors. All pyrovalerone-cathinones present with similar pharmacological profiles. They all exhibit inhibitory potencies at DAT and NET equal/greater than cocaine (Baumann et al., 2013b); or methamphetamine (Aarde et al., 2013); do not induce monoamine release; readily cross the blood-brain barrier (BBB) owing to their high lipophilicity (Simmler et al., 2013b; Eshleman et al., 2013). Due to these characteristics, these molecules may present with a high abuse potential (Schifano et al., 2016a).

Interestingly, the para-substituted cathinones e.g. 4-MEC, flephedrone, mephedrone, 4-bromomethcathinone exhibit a greater serotonergic effect than their amphetamine analogues with flephedrone (4-fluro-cathinone) exhibiting the lowest serotonergic effect in this group (Rickli et al., 2015). This example shows the impact of substituting various functional groups at different positions on existing cathinone molecular scaffolds. For example, four types of chemical scaffold for cathinones were identified by Zdrazil et al. (2016) highlighting structural variations including substituents of the nitrogen atom, the aromatic ring and the keto group carbon. These variations have been shown to affect selectivity at DAT and SERT (Figure 1) (Zdrazil et al., 2016).

< Figure 1 about here >

3.3.1. Cathinones in combination with remaining recreational drugs; pharmacological interactions

In most cases, users of cathinones take other drugs as well on the same occasion (Schifano et al., 2016b), and one could wonder about the rationale of this polydrug abuse. Indeed, cocaine and/or amphetamines and/or ecstasy tablets may be taken in combination with cathinones to maintain arousal and a state of alertness, since the MDMA/serotonergic stimulant entactogenic effects fade away in a few hours (Schifano, 2004). Potential interaction of cathinones could theoretically occur with prescribing medications as well, e.g. with the monoamine oxidase inhibitor moclobemide, which is taken to enhance the effects of ecstasy-like stimulants (Vuori et al. 2003); or with selective serotonin reuptake inhibitors (SSRIs). These interactions could facilitate occurrence of the serotonin syndrome (Green et al., 1995), which can be fatal (Schifano, 2004). Serotonergic release is intensified by

parallel use of dopaminergic stimulants, with the more serious complications (e.g. delirium, seizures, coma) occurring when serotonergic stimulants are self-administered together with cocaine and amphetamines (Huether et al., 1997; Schifano, 2004). Moreover, the mixed use of hallucinogens (i.e. ketamine and/or LSD) together with stimulants/cathinones can increase occurrence of idiosyncratic/intoxicated 'behaviour', such as dangerous driving, with a consequent higher risk of a fatal outcome. Finally, it is also possible that concurrent use of sedatives (i.e. opiates) might somewhat mitigate the excess of sympathomimetic overactivity observed with stimulants, including cathinones (Schifano, 2004).

3.4. Toxicity of cathinone mixtures

Since the mode of action of newly emerging cathinones is not fully understood, toxicity intrinsic to individual cathinones or cathinone mixtures is unknown and unpredictable. A survey conducted in a UK emergency setting reported that the number of toxicities resulting from the abuse of NPS increased from seven in 2006 to 98 in 2010. 82 of these cases showed toxicities resulting from the abuse of synthetic cathinones (Wood et al., 2013). The Euro-DEN Plus project reported that two-thirds of hospital admissions involving NPS were related to cathinones (EMCDDA, 2016a). Adverse effects related to cathinones could be predicted from their pharmacological activity. For example, the intake of high or multiple doses of the methamphetamine-like cathinones may induce hypertension, hyperthermia, euphoria, hallucinations (Aarde et al., 2011; Liechti, 2015). If both MDPV and methamphetamine are taken together, they may induce sympathomimetic toxicity and would bear a high risk of addiction. In addition, the pyrovalerone-like cathinones such as MDPV and α-PVP may induce agitation and hallucination (Spiller et al., 2011; Eiden et al., 2013). Since MDPV is 10 times more potent than cocaine, it was postulated that it can induce severe hypertension and tachycardia and is associated with a high potential for abuse (Baumann et al., 2013a).

Furthermore, in-silico studies could be performed to predict cathinone toxicity. For example, molecular modelling studies conducted by Gibbons and Zloh (2010) demonstrated that Me-cathinones were less lipophilic than corresponding methamphetamine analogues. The log P and log BBB (blood brain barrier) values of Me-cathinones were lower than that of methamphetamine with at least one log unit (Gibbons & Zloh, 2010). This demonstrated lower ability to cross the BBB than methamphetamines. For this reason, and as confirmed in drug surveys, drug users often consume higher doses of cathinones with low lipophilicity (e.g. mephedrone), which could result in repeated dosing (Schifano et al., 2016b) and inadvertent overdoses, toxicities and potential fatalities. Mephedrone has been implicated in fatalities, intoxications resulting from high concentrations and impaired driving (Cosbey et al., 2013). However, methamphetamine has been shown to affect the BBB permeability, hence facilitating the passage of co-ingested NPS to the brain (Northrop & Yamamoto, 2015). On the other hand, pyrrolidine analogues such as MDPV contain a pyrrolidine group and a tertiary amine group, which infer high lipophilicity and low polarity and hence, high permeation across the BBB may potentially occur (Coppola & Mondola, 2012a; Gibbons & Zloh, 2010; Lewin et al., 2013; Simmler et al., 2013b).

Toxicity resulting from the adulteration of illicit drugs has also been widely reported (Giné et al., 2014). For example, methylone and butylone, two SSRIs, found in a tablet sold as ecstasy, induced serotonin syndrome and death (Warrick et al., 2012). Another case involved the ingestion of both methylone and ethcathinone, also SSRIs, sold in a tea-bag as 'legal ecstasy'. The mixture was implicated in the induction of syndrome of inappropriate secretion of anti-diuretic hormone (SIADH), seizures and rhabdomyolysis (Boulanger-Gobeil et al., 2012). Methylone and methamphetamine have been shown to have synergistic toxic effects on Chinese hamster ovary cells, a heterologous system, which expresses monoamine transporters (Sogawa et al., 2011). Alternatively, methylone and methamphetamine mixtures do not induce an increase in the release of monoamines from chromaffin granules (Sogawa et al., 2011). Mephedrone and MDPV have been shown to have additive effects, which may prolong toxicity (Cameron et al., 2013).

Consequences of poly-drug intake can lead to the increased risk of toxicity, overdose, death and crimes (homicides, robberies and sexual assaults) (Rojek et al., 2014; UNODC, 2014). Poly-drug ingestion was found to be associated with multi-drug resistance, as well as the risk of blood-borne and sexually transmitted infections (Wagner et al., 2014). The effect of co-ingestion of multiple cathinones or cathinones combined with adulterants, in cathinone mixtures, is unknown and unpredictable; especially given that the actual consumed doses, the actual active drug concentrations in the products ingested, potency, routes of administration, time of onset and the duration of action are not always known. For instance, a death case was related to two NPS products 'aroma liquid' and bath salts' and alcohol. Three cathinones (i.e. 4-MeO-PV8, PV9 and 4-MeO-PV9) and diphenidine were contained in the products and were directly implicated in the cause of deaths, under the influence of three co-ingested benzodiazepines and alcohol (Kudo et al., 2015). Another case reported by Klavž et al. (2016), where a patient attempted suicide following the sequential ingestion of a number of synthetic cannabinoids and cathinones namely AB-CHMINACA, AB-FUBINACA, α-PHP, α-PVP and 4-CMC in addition to his regular prescription medicines.

The implications of high-risk practices particularly injecting mixtures can be detrimental. For example, the injection of a 'bath salts' product found to incorporate the cathinone 4-MeO-PV8 and the opioid acetyl fentanyl has resulted in the amphetamine-user's death (Yonemitsu et al., 2016). The co-administration of mephedrone with heroin led to the death of a 22-year-old Caucasian man (Dickson et al., 2010). The National Programme on Substance Abuse Deaths (NPSAD) reported many cases of poly-drug use involving mephedrone, where these combinations were implicated in the cause of deaths. These combinations include mephedrone taken with alcohol; alcohol and other drugs, cannabis, stimulants, diazepam, opiates, piperazines, GBL/ GHB, ketamine, methcathinones, antidepressants, antipsychotics, anti-epileptics, hypnotics and sedatives other than diazepam (Corkery et al., 2012). A large study retrospectively reviewed the toxic effects of NPS using post-mortem results and criminal casework from January 2010 to December 2012. Results showed that 41% of deaths, where cathinones were implicated, resulted from hangings and mechanical suicides (Blum et al., 2013; Elliott & Evans, 2014). This is in line with the NPSAD findings (Corkery et al., 2012).

3.5. Symptoms of intoxication by cathinones

Cathinone-related calls to a US poison centre rose sharply from 303 in 2010 to 4720 in 2011 (Jerry et al., 2012) and the symptoms of cathinone intoxication have been extensively published (Coppola & Mondola, 2012a; Khullar et al., 2014; Lewin et al., 2013). Neuro-psychological toxicity is thought to be induced as a result of impairing the function of the central monoamine transporting system (German et al., 2013). Neuro-psychological symptoms have been shown to be associated with previous exposure to other stimulants such as cocaine and methamphetamine (Spiller et al., 2011). Psychiatric symptoms include agitation, aggression, anxiety, combative behaviour, confusion, extreme paranoia, delusions, hallucinations, paraesthesia, self-harm and harm to others; cardiovascular symptoms mainly include sympathomimetic symptoms such as narrow-complex tachycardia, ventricular tachycardia, ventricular fibrillation, systemic hypotension, palpitations, peripheral vasoconstriction, hypertension, chest pain, ECG abnormalities (Jerry et al., 2012; Home Office, 2015; Regan et al., 2011; Toxbase, 2014); neurologic symptoms include seizures (particularly myoclonus), headache, and tremors; metabolic and blood tests abnormalities: elevated creatine kinase and hypokalaemia; adverse effects lasting more than 24 hours (Jerry et al., 2012; Spiller et al., 2011); acidosis (Toxbase, 2014); other symptoms include: hyperthermia, blurred vision, mydriasis, nausea and vomiting, abdominal pain, bruxism, excess sweating (Spiller et al., 2011). Multi-cathinone intoxication reported to Toxbase included symptoms of serotonin syndrome, stroke, myocardial infarction, hyponatraemia, rhabdomyolysis, renal and hepatotoxicity, pulmonary oedema, cardiomyopathy, convulsions, raised body temperature, coma and deaths (Toxbase, 2014).

3.6. Proposed treatments of cathinone poisoning

Detection of an NPS poisoning, identification of the type and quantity of NPS consumed are key to determining antidotes and supportive adjunct treatments to save lives and prevent additional fatalities caused by unknown NPS (Motto, 2012). There are no selective rapid tests to detect NPS in biological fluids, making targeted treatment more challenging (Abdulrahim & Bowden-Jones, 2015). The unknown composition of NPS mixtures represents a great challenge to the prediction of pharmacokinetics and extent of toxicity may result in a plethora of 'behavioural and psychopathological disturbances' (Khullar et al., 2014; Schifano et al., 2015). Due to lack of universal treatment guidelines, lack of users' cooperation and detection limitations of current test tools, it is challenging to identify newly emerging NPS. This, in turn, affects treatment decisions and patients presenting to emergency departments following exposure to unknown NPS usually receive supportive treatment for symptom management only (Schifano et al., 2015). However, one of the biggest challenges is associating specific compounds with symptoms, which is required to accurately assess harms, and thus educate and legislate.

Holistic interventions include psychosocial interventions to influence behaviour change and promote abstinence (Abdulrahim & Bowden-Jones, 2015). In addition, psychological treatment for co-occurring mental health issues can be offered (Abdulrahim & Bowden-Jones, 2015). Based on the NEPTUNE guidelines (Novel Psychoactive Treatment UK Network), the only available treatment guidelines to date, suggested treatment of acute and chronic harms resulting from the intake of NPS depends on NPS classes. The NEPTUNE guidelines has classified NPS into four categories: stimulants, depressants/ dissociatives, hallucinogens and synthetic cannabinoids (Abdulrahim & Bowden-Jones, 2015).

In general, treatment may include antidepressants (to control mood disorder), hypnotic-sedatives (to control agitation), vitamins and nutrients (to prevent encephalopathy) (Newcombe, 2013) and naloxone (Atreya et al., 2013). Supportive care suggested by Toxbase (2014) include: using diazepam or haloperidol for agitation and delirium, diazepam or midazolam for seizures, sodium bicarbonate for metabolic acidosis, nitrates or rate-limiting calcium channel blockers for hypertension, vasopressors and ionotropes for hypotension, cooling techniques for pyrexial patients, haemodiafiltration could be used to filter myoglobin in case of rhabdomyolysis. Other supportive treatments given to nine cases showing toxicity with 'bath salts' included: midazolam, lorazepam, diazepam and etomidate given for agitation; naloxone; ice packs for hyper/ hypothermia and intravenous replacement fluids for dehydration (Motto, 2012). MDPV-related intoxications were managed using antipsychotics or benzodiazepines (EMCDDA-Europol, 2014). Sympathomimetic and psychotic signs and symptoms of MDPV-related intoxication resolved after 3-4 days (EMCDDA-Europol, 2014). Targeted treatment suggested by Velez and Benitz (2015) include intramuscular or intranasal midazolam, intramuscular lorazepam or intravenous diazepam to control aggression and agitation. If benzodiazepines cannot control the patients, then propofol could be used. Haloperidol, droperidol, aripiprazole, quetiapine, risperidone and olanzapine could be used to control psychosis. Intravenous fluid administration is suggested to treat hyperthermia and control rhabdomyolysis. Both benzodiazepines and cyproheptadine could be used for the management of SIADH (Velez & Benitz, 2015). Psychosocial interventions are the mainstay of treatment (DH, 2007). Benzodiazepines have proved to be useful adjunct to treatment (Nelson et al., 2014b).

Raising confidence of healthcare professions in managing toxicity resulting from NPS is still needed (Wood et al., 2016). Therefore, raising awareness and education of healthcare professionals on NPS health harms, interventions, harm reduction techniques and referral pathways is of paramount importance (Guirguis et al., 2015).

4. Conclusions

The effect of the combined intake of cathinone products, whether simultaneous or sequential, could be detrimental to individuals' health. This is because individual NPS products may induce severe toxicity, not to mention the dose, the concentration, the potency and the potential interactions that may occur between the drugs consumed. Inconsistencies in the composition of identical branded

cathinones and the reduced purity pose unpredictable public health risks and highlight the challenge faced by front-line healthcare staff and law enforcement agents. In addition, heterogeneity of NPS products and the limitations of the current detection tools highlight the existing need for efficient on-site screening and detection. More research is needed to understand the health impact of cathinone mixtures' intake. Raising awareness and education among users, the general public and frontline staff and the development of harm reduction techniques is of paramount importance to tackle the flood of NPS.

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Contributors

Data collection was undertaken by AG and assisted by JC. AG conceived the paper, undertook case identification, data preparation and analysis, and led on writing. JC advised on data sources; MZ provided information on molecular aspects of cathinones; FS contributed information on pharmacology and treatment. JS, SK, JC and FS reviewed the paper. All authors contributed to the writing of the paper**.**

Conflicts of interest

No conflicts of interest are declared here that may have influenced the interpretation of present data. Please note the following: FS is a full member of the UK Advisory Council on the Misuse of Drugs (ACMD); FS and JC are members of the ACMD's NPS and Technical Committees. The views expressed here are solely those of the authors, and do not necessarily reflect those of the Home Office or the ACMD.

Ethics

No ethics approval was required since the research involved secondary analysis of published data.

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Table 1: Examples of branded NPS products containing a cathinone and other constituents

Product name	Cathinone mixtures identified	Reference
Blast	Flephedrone and caffeine	(Araújo et al., 2014)
Bliss	Methedrone, pentedrone, 3,4-DMMC, caffeine and isopentedrone	(Araújo et al., 2014)
Bloom	Methylone, 4-MEC, pentedrone, dimethocaine and isopentedrone	(Araújo et al., 2014)
Bloom	Methedrone, pentedrone, ethcathinone, caffeine, and isopentedrone	(Araújo et al., 2014)
Bloom	Methedrone, pentedrone, caffeine, ethcathinone and isopentedrone	(Araújo et al., 2014)
Blow	4-MEC, MDPV and 3-MEC	(Araújo et al., 2014)
Blow	4-MEC, MDPV, caffeine and 3-MEC	(Araújo et al., 2014)
Charlie	Buphedrone, ethcathinone and caffeine	(Araújo et al., 2014)
Charlie	Buphedrone and ethcathinone	(Araújo et al., 2014)
Duffy's		
Hysceria	Naphyrone and caffeine	(Kavanagh et al., 2010)
e Blast	4-MEC, alpha-PVP, MDPBP andD2PM	(Leffler et. al., 2014)
Exotic Super		
Strong	4-MEC, α-PVP, MDPBP, 4-MPPP and D2PM	(Leffler et al., 2014)
Flake	Dimethocaine, butylone and lidocaine	(Kavanagh et al., 2010)
Jet	4-fluoromethcathinone and an unknown saccharide	(Leffler et al., 2014)
Kick	Pentedrone, isopentedrone and methylamine	(Araújo et al., 2014)
Kick	Buphedrone and caffeine	(Araújo et al., 2014)
Magic	Benzocaine, caffeine and mephedrone	(Kavanagh et al., 2010)
Neodove	mephedrone, caffeine, N-ethylcathinone and α-phtalidomipriophenone	(Camilleri et al., 2010)
NRG2	4-MEC and trace mephedrone	(Ayres & Bond, 2012)
Ocean Burst	Ethcathinone, butylone and 4-MEC	(Leffler et al., 2014)
Platinum	Naphyrone and caffeine	(Kavanagh et al., 2010)
Pure NRG	Naphyrone and caffeine	(Kavanagh et al., 2010)
Rush	Pentedrone, caffeine, isopentedrone and methylamine	(Araújo et al., 2014)
Rush	Buphedrone, caffeine and methylamine	(Araújo et al., 2014)
Sub Coca 2	α-phtalidomipriophenone and 2-fluoromethamphetamine	(Camilleri et al., 2010)
Sub Coca	mephedrone, caffeine, N-ethylcathinone and α-phtalidomipriophenone	(Camilleri et al., 2010)
Vanila Sky	MDPBP, MDPV and lidocaine	(Kavanagh et al., 2010)
White Fizz	3',4'-methylenedioxy-α-pyrrolidinobutiophenone (MDPBP), Benzedrone, caffeine, 4-MEC and pentylone	(Kavanagh et al., 2010)
White ice	3-flephedrone, caffeine, lidocaine	(Christie et al., 2014)

Figure 1: Four cathinone scaffolds. Based on Zdrazil et al. (2016) (ChemDraw 15.0)