

ACMD

Advisory Council on the Misuse of Drugs

Consideration of the cathinones

ACMD

Advisory Council on the Misuse of Drugs

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Rt Hon Alan Johnson MP
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31st March 2010

Dear Home Secretary,

I have pleasure in attaching the Advisory Council on the Misuse of Drugs report on the 'Consideration of the cathinones'.

The ACMD recommends that the cathinone compounds be brought under control of the Misuse of Drugs Act 1971 in Class B, Schedule I by way of a generic definition. Based on the attached evidence and by analogy with the amphetamines, the ACMD consider that the harms associated with the cathinones most closely equate with other compounds in Class B.

The ACMD also recommend that particular attention is focussed on credible and consistent public health messages that are promulgated both to the public and health professionals – the latter for the purposes of providing advice.

The ACMD is concerned that, particularly in the case of mephedrone, the internet plays a significant part in the marketing, sale and distribution of the drug and social networking sites may also play a role. The ACMD therefore believes that resources should initially be focussed on supply side activities with a concurrent emphasis on educating users of this drug so as to highlight the real dangers of mephedrone and the cathinones.

The ACMD indicated, in its letter to the Home Secretary, of the 22nd December 2009, its concerns about the sale of mephedrone and its plans for review. However, the rapid increase in the use of mephedrone in the UK has been exceptional. This sudden rise in prevalence of what we consider to be a harmful drug has brought to the fore our concerns that we need to consider a range of options for limiting the rapid spread of such substances. The ACMD intend to provide you with further advice on the possible control of 'legal highs' concerning recommendations and advice that is broader than the scope of

what either this report or that on other individual or classes of compounds will allow.

In addition, I would like to draw your attention to further advice that we will provide on the naphthyl analogues of pyrovalerone and other such analogues. The ACMD will meet to discuss other compounds that are not covered by this generic scope in the next few weeks.

Yours faithfully,

A handwritten signature in black ink, appearing to read "Les Iversen". The signature is written in a cursive style with a large initial 'L'.

Professor Les Iversen FRS

1. Background

- 1.1. In March 2009 the then Home Secretary requested advice from the ACMD on so called 'legal highs'. The ACMD have looked at a number of substances to date and provided advice on the piperazines and the synthetic cannabinoids ('Spice'). The ACMD wrote to the Home Secretary in December 2009 (Annex D) setting out the ACMD's concerns regarding the cathinones and mephedrone in particular, which first came to the ACMDs attention in the summer of 2009. On the 2nd February 2010 the ACMD Chair (Professor Les Iversen) met with the Home Secretary to further discuss the issue and to provide an update.
- 1.2. The ACMD gathered evidence on the cathinones at a special meeting of the Technical Committee (22nd February 2010) and discussed additional evidence and possible recommendations at a further Technical Committee meeting on the 25th March 2010, and at the ACMD Council meeting on the 29th of March 2010.

2. Introduction

- 2.1. Cathinone is one of a number of alkaloids which can be extracted from the (fresh) leaves of *Catha edulis* (khat). It is structurally very similar to amphetamine (1-phenylpropan-2-amine) and represents the β -keto analogue of amphetamine.
- 2.2. Cathinone (Class C), methcathinone (Class B), diethylpropion (Class C) and pyrovalerone (Class C) are controlled under the Misuse of Drugs Act 1971. The three controlled cathinone derivatives are listed in the United Nations Convention on Psychotropic Substances (1971) and have been reviewed by the WHO Expert Committee on Drug Dependence (WHO, 1995). However, other derivatives and analogues are not presently controlled (including mephedrone). Notwithstanding the potential harms of the cathinones it is apparent that mephedrone and other cathinones are being sold without any apparent effective regulation.
- 2.3. The ACMD has communicated its intentions to review the cathinones to the Home Secretary, over recent months, through meetings and correspondence (see the ACMD's letter of the 22nd Dec 2009 – Annex D). The ACMD has been concerned about the rise in prevalence of the cathinones and potential harms initially through reports from drug services, young people's treatment services, head teachers, drug surveys, the police and media, among others.
- 2.4. Other countries (including: Sweden Denmark, Norway, Ireland and Israel) have recently controlled specific cathinones. However, we are not aware of any country that has developed generic legislation to control the cathinones as a class.
- 2.5. The ACMD is aware of the collation of data on mephedrone by Europol and the EMCDDA in the form of a joint report under Article 5.1 of Council Decision 2005/387/JHA. The ACMD wrote to the UK focal point (the Reitox NFP) that would be providing information as requested by Article 5 of the Decision.
- 2.6. This report is compiled from oral and written evidence considered at the meetings (paragraph 2.3) above. A full citation of the evidence received and considered is provided in Section 10 and submitting individuals and organisations are given in Annex C.

3. Chemistry and pharmacology

Chemistry¹

- 3.1. Cathinone (2-amino-1-phenyl propanone) is one of a number of alkaloids which can be extracted from the (fresh) leaves of *Catha edulis* (khat). However, the ACMD understands that most of the cathinones seized, and those that have been tested, are synthetic in origin.
- 3.2. Cathinone is structurally very similar to amphetamine (1-phenylpropan-2-amine), differing only in the functionality present at the β -carbon. Cathinone possesses a ketone oxygen at the β -carbon; cathinone can therefore be considered as the ' β -keto analogue' of amphetamine (see Figures 1 and 2).

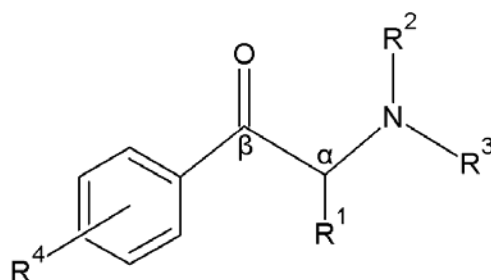
Figure 1: The structural similarity between amphetamine (left) and cathinone (right)



- 3.3. Structural modifications to the 1-phenylpropan-2-amine (amphetamine) backbone have produced a range of different compounds, many of which are closely related structurally to amphetamine; these are known as the 'amphetamines'. In a similar manner, the molecular architecture of 2-amino-1-phenyl propanone (cathinone) can be altered to produce a series of different compounds which are closely structurally related to cathinone. Together these are known as the 'cathinones' or 'cathinone derivatives'.
- 3.4. The *N*-methyl derivative known as methcathinone or ephedrone is the cathinone analogue of methylamphetamine, while 3,4-methylenedioxymethcathinone (methydone) is the cathinone analogue of MDMA (ecstasy); 4-methylmethcathinone (mephedrone) has no commonly used amphetamine equivalent.
- 3.5. The basic cathinone structure (see Figure 2) can be altered in a number of predictable ways, such as the inclusion of additional functionality to the aromatic ring (ring substitution, R⁴), *N*-alkylation (or inclusion of the nitrogen atom in a ring structure, R² and R³), and variation of the (typically alkyl) α -carbon substituent (R¹). Multiple modifications may of course be present in a single derivative; cathinones are all usually *N*-alkylated (or the nitrogen is incorporated into a ring structure, typically pyrrolidine) and many also bear ring substituents.

¹ White, 2010.

Figure 2: Generic sites for structural variation of cathinone, detailing α and β positions².



- 3.6. The genesis of synthetic cathinone chemistry is rooted in the synthesis of cathinone over 120 years ago. Since this time, many synthetic cathinones have been reported, the vast majority of which have not been used in a medicinal setting. However, a handful of cathinones, such as diethylpropion, bupropion and pyrovalerone have been used in pharmaceutical preparations, and the properties of novel cathinones (such as naphthylpyrovalerone (Meltzer *et al.*, 2006)) is still an area of active research.
- 3.7. Bupropion (page 42) is used medically as an antidepressant and an aid to smoking cessation and is a prescribed drug, marketed under the trade name Zyban®. Although it is a ring substituted cathinone no samples of Bupropion have been encountered in forensic analysis of seizures in the UK, and there is no evidence for its misuse.
- 3.8. The misuse of selected synthetic cathinones is not new; methcathinone (ephedrone), originally used as an antidepressant in the former Soviet Union in the 1930's, went on to be used recreationally there (especially during the 1970s and 1980s) and in the USA (1990s). The emergence of six synthetic cathinones in Germany was reported between 1997 and 2004. All six substances bear an α -pyrrolidino functionality and are therefore closely related to pyrovalerone (page 41).
- 3.9. More recently, there have been an increasing number of reports of other synthetic cathinones encountered within the European Union. Although many of these compounds are simply β -keto analogues of well-known amphetamines, the presence of the ketone functionality often circumvents any control measures which may already be in place for the related

² The generic cathinone backbone (see Figure 2) possesses a chiral centre (the α -carbon atom if R¹≠H); cathinone and its derivatives can therefore exist as stereoisomers, the potencies of which may be markedly different. Although it is the *S*-enantiomer of cathinone which is found in the fresh leaves of *Catha edulis*, the chirality of the cathinones is not determined during routine forensic analysis of seizures. There is, however, no evidence to suggest that the synthetic cathinones currently available are enantiopure; it is instead likely that they are supplied as racemic mixtures. The qualitative or quantitative differences between the enantiomers of the non-controlled cathinones is not known.

amphetamine congeners. Since 2006, the following cathinones have been reported in the European Union (see Table 1; for the position of the substituents R¹ to R⁴, see Figure 2). According to data from UK forensic providers, since January 2006 six of these have been encountered in the UK (emboldened in Table 1).

Table 1: Some of the non-controlled cathinones encountered in the European Union since 2006 (excluding reports of pyrovalerone derivatives from 1997-2004). those in bold type have been encountered in the UK.

Name	Common name	R ¹	R ²	R ³	R ⁴
<i>N,N</i> -dimethylcathinone		Me	Me	Me	H
Ethcathinone		Me	Et	H	H
4-Methylmethcathinone	Mephedrone	Me	Me	H	4-Me
Bk-PMMA	Methedrone	Me	Me	H	4-MeO
4-Fluoromethcathinone	Flephedrone	Me	Me	H	4-F
3-Fluoromethcathinone		Me	Me	H	3-F
bk-MDMA	Methylone	Me	Me	H	3,4-methylenedioxy
bk-MDEA	Ethylone	Me	Et	H	3,4-methylenedioxy
bk-MBDB	Butylone	Et	Me	H	3,4-methylenedioxy
MDPV	Methylenedioxyprovalerone	<i>n</i> -Pr	pyrrolidinyl		3,4-methylenedioxy

3.10. Of the total number of cathinone derivatives encountered by UK forensic providers, by far the most commonly encountered is 4-methylmethcathinone (mephedrone) (89% of seizures). However, data from the Forensic Science Service indicate that cathinones accounted for a very small fraction of Police seizures submitted in 2009. Tentative data also indicate a rapid rise in the number of cathinone submissions during 2009, with a concomitant decrease in the number of piperazine submissions.

3.11. Data from UK forensic providers suggest that the cathinones are normally submitted as either white or brown powders³; data from January 2006 to mid-February 2010 indicate that, of all cathinone derivatives submitted, 95% were in powder form, 4% being submitted as tablets or capsules.

3.12. Purity data for the cathinones are not available from UK forensic providers, since it is not usually determined during routine forensic analysis. However, cathinones are normally advertised as being of 'high purity', typically >95%. Some adulterants, including benzocaine, lignocaine, caffeine and paracetamol, have been detected in a small proportion of seizures of the cathinones. Some submissions have been adulterated with controlled drugs such as cocaine, ketamine, amphetamine and 1-benzylpiperazine (BZP), although these are rarely encountered.

³ The freebase forms of the cathinones are unstable and readily decompose; the cathinones are normally encountered as the hydrochloride salts.

- 3.13. There are currently no colorimetric field tests available to identify all of the cathinone derivatives, although some chemical tests, such as the Simon's test and Chen test may be used to give an indication of the presence of a small number of the cathinones. More specific field tests based on immunoassay technology are not yet available⁴.
- 3.14. As with the amphetamines, both systematic (IUPAC) and non-standard nomenclature is common in cathinone chemistry. Often, the assimilation of a common structural motif is reflected in non-standard nomenclature. Thus, structural incorporation of the '2-methylamino-1-phenyl-1-propanone' fragment, which is also known as methcathinone or 'ephedrone', is often indicated in nomenclature; 4-methylmethcathinone is 'mephedrone' and 4-fluoromethcathinone is 'flephedrone'. The use of acronyms is also widespread; 3,4-methylenedioxypropylamphetamine is known as 'MDPV', whilst α -pyrrolidinopropiophenone, one of a number of α -pyrrolidino cathinones, is simply known as α -PPP. As a consequence of the β -keto substituent, it is also common practice for widely accepted amphetamine acronyms to be augmented with the prefix 'bk'. For example, 3,4-methylenedioxymethcathinone (methylone), the cathinone analogue of MDMA, is often referred to as 'bk-MDMA'. Mephedrone [2-(methylamino)-1-(4-methylphenyl)-1-propanone] is the most commonly used cathinone derivative and forms the focus of this report.

Pharmacology

- 3.15. As with the amphetamines, the cathinones act as central nervous system stimulants, although the potencies of the cathinones are generally lower than their amphetamine congeners, probably because the increased polarity conferred on a cathinone by the presence of a β -keto group reduces their ability to cross the blood-brain barrier.
- 3.16. Several cathinones have been used as active pharmaceutical ingredients (API). Bupropion has been used as an antidepressant, and as an aid to stop smoking cigarettes. Diethylpropion (Amfepramone) and propylhexedrine have both been proposed as appetite suppressants, although they are not currently in clinical use. 4-methylmethcathinone (mephedrone), the most commonly encountered synthetic cathinone derivative in the UK, has never been used as an API or patented as a potential API.
- 3.17. Little data are available on either the pharmacokinetics or pharmacodynamics of the cathinones. Research on the metabolism of the ring-substituted cathinones bk-MBDB and bk-MDEA has implicated *N*-dealkylation, demethylenation followed by O-methylation and β -keto reduction as major metabolic pathways (Zaitsev *et al.*, 2009).

⁴ Colorimetric tests based on the Marquis reaction cannot be used to identify all of the cathinone derivatives. Some chemical tests, such as the Simon's test and Chen test may be used to give an indication of the presence of a small number of the cathinones.

- 3.18. The effects of cathinones bearing ring-substituents in human subjects are reportedly similar to those of cocaine, amphetamine and MDMA (Table 2; CairScotland, 2010). Self reported subjective effects of ring-substituted cathinones include:
- Feelings of empathy (openness, love, closeness, sociability, well-being);
 - Stimulation / alertness / rushing;
 - Euphoria / mood lift / appreciation of music; and,
 - Awareness of senses.
- 3.19. Studies of the effects of cathinones on monoamine neurotransmission in rat brain confirm their mechanisms of action to be similar to those of the amphetamines. Both groups of drugs bind to monoamine transporters for dopamine, serotonin and noradrenaline (norepinephrine) in brain and promote release of these monoamines (Cozzi *et al.*, 1999; Nagai *et al.*, 2007). As with the different amphetamines, individual cathinone derivatives vary in their relative potencies as inhibitors of the three monoamine transporters – summarised in Table 2. There are no published data on the effects of mephedrone on monoamine transporters, but it may be expected to be intermediate in its profile between methcathinone and methylone.

Table 2. Actions of selected drugs on monoamine transporters*

	Dopamine	Serotonin	Noradrenaline
Amphetamine	+++	+	++++
MDMA	++	+++	+++
Cathinone	+++	++	+++
Methcathinone	+++	+	+++
Methylone	++	+++	++++
Mephedrone	?	?	?

*Data from Cozzi *et al.*, (1999) and Nagai *et al.*, (2007). Values are depicted as relative affinities since the studies did not use the same units. + = low affinity; ++++ = highest affinity.

- 3.20. It is notable that the cathinones examined were potent inhibitors of the noradrenaline (norepinephrine) transporter (NET). This helps to explain the strong sympathomimetic⁵ actions of cathinones – due to their ability to promote release of noradrenaline from the sympathetic nerves in various peripheral organs, notably the heart and vascular system.
- 3.21. Cathinone and methcathinone are amphetamine-like behavioural stimulants. When administered to experimental animals they cause hyperactivity, with methcathinone being approximately 10 times more potent than cathinone (Feyissa and Kelly, 2008; Glennon *et al.*, 1987)

⁵ mimicking stimulation of the sympathetic nervous system

3.22. When administered *in vivo* to rats trained to recognise and to distinguish the subjective effects of amphetamine, the animals cross-generalised completely to methcathinone (i.e. they were unable to recognise this substances as having different effects from amphetamine). Methylone, however, showed only weak cross generalization to amphetamine, but cross generalized completely to MDMA in rats trained to recognize this as the discriminative stimulus (Dal Cason *et al.*, 1997).

4. Epidemiology of cathinone use and methods of use

Availability and use

- 4.1. Many of the cathinone compounds, particularly mephedrone, can be purchased from many different sources, and are readily available over the internet. Although the provenance of the substances is often not clear, several suppliers source compounds from China (Ramsey, 2010; UK Border Agency, 2010). Exercises at Heathrow targeting air courier traffic from China for delivery to UK domestic addresses gave rise to seizures of mephedrone. Claims of manufacture in a number of other countries are made on the internet.
- 4.2. Intelligence from Australia Customs and Border Protection Service has identified China and the UK as being the principal source of mephedrone. However, it is likely that in the case of the UK, this represents transit of the drugs and not necessarily production in the apparent country of origin.
- 4.3. Mephedrone and other cathinones are predominantly sold over the internet and in 'head shops'. Websites selling cathinone based compounds – generally mephedrone - normally exhibit a disclaimer that the compounds 'are not for human consumption'. Instead, they are sold as research chemicals, 'novelty bath salts' (3-fluoromethcathinone) or, more commonly, as plant food/plant growth regulators (Sumnall, 2009). However, none of the cathinones has any recognized efficacy as a plant fertilizer nor would they suitably function as bath salts.
- 4.4. Slang terms for some of the cathinones include *Bubble(s)*, *miaow*, *meow meow*, *4-MMC*, *Mcat*, *sub-coca*, *toot* and *Top Cat*.
- 4.5. Cathinones (generally mephedrone) are usually sold as white or brown powders, sometimes as capsules, or more rarely as pills, and are often advertised as being of 'high' purity (> 95%). CairScotland (2010) report that '*Bubbles*' was originally sold in capsules, but now more often in 1g bags. Reports suggest varying prices: around £10-15/g if purchased from 'headshops', clubs or dealers (Druglink, 2010; Linell, 2010).
- 4.6. Self-reported dosages range from 5 mg or less (for MDPV) to 200 mg or more (for mephedrone), with some mephedrone users reporting 're-dosing' (bingeing) to prolong the euphoric experience, leading to 1-2g being consumed in a session. The cathinones are sometimes used in conjunction with alcohol or controlled substances; co-abused substances include cocaine, cannabis, ketamine and MDMA. Studies of polysubstance use with the cathinones are not available, however, it should be noted that polydrug use is increasingly a feature of UK illegal consumption patterns more generally.
- 4.7. The reason for the apparent emergence and sudden increase in mephedrone use in the UK in 2009 is unclear. However, interviews with users and community workers (Newcombe, 2010; Measham *et al.*, 2010, NME, 2010) suggest that the unavailability and/or low purity of cocaine

and MDMA in 2009 (Hand and Rishiraj, 2009) have contributed to the increase in mephedrone use. In addition, the cathinones are presently a legal alternative to other drugs and are widely available from internet websites.

- 4.8. Mephedrone powder may be snorted (insufflated) (sometimes by keying⁶ – approximately 5-8 keys per gram (Linell, 2010)). The drug may also be swallowed – often after wrapping in tissue paper (bombing or dabbing) or, more rarely, injected (CairScotland, 2010; Linell, 2010; McVean, 2009; Measham *et al.*, 2010).
- 4.9. Reports from users presenting at hospital A&E units are that mephedrone is taken in staggered doses (Wood *pers. comm.*).
- 4.10. Emergent research with mephedrone users suggests that they may appear to develop tolerance quickly and as a consequence tend to consume higher doses more frequently.
- 4.11. Evidence from the Bailiwick of Guernsey Customs report an increase in the prevalence of mephedrone from seizures and this has superseded the seizures of 'Toot' (identified predominantly as Butylone and methylone) (McVean, 2009 and 2010). It is reported that mephedrone and 'Toot' are being injected by users and has become popular among users of heroin (McVean, 2009 and 2010).

Prevalence and reported data

- 4.12. There are little published data on the prevalence of the cathinones; most available data are from self reported surveys of particular demographics.
- 4.13. Since many of the cathinones are not controlled, they are not included in the 'stimulant' group of substances in the British Crime Survey (BCS). However, we understand that the BCS will now include a specific question on mephedrone – interim data should be available to the ACMD after 6 months of the question becoming part of the survey.
- 4.14. The Mixmag survey (Winstock, 2010) is a cross sectional, self reported, self nominating, survey of over 2,000 UK individuals using the online website "Don't Stay In" for the dance magazine Mixmag⁷. The most recent survey included a question on mephedrone. Of self reported drug use, mephedrone was the fourth most commonly used drug in the last month (Cannabis (any), ecstasy (any) and cocaine powder ranked higher in terms of % use in the last month). The survey data show that 41.7% of respondents indicated they had ever used mephedrone, 33.6% in the previous month. These data suggest that the use of mephedrone is a new phenomenon since lifetime and past month prevalence is so similar in this survey. The synthetic cathinone methylone had been tried by 7.5% of respondents in the last month and 10.8% in their lifetime. Also other

⁶ Keying is the activity by which a user dips a key into a bag of the powdered drug and then insufflates (snorts) off the key.

⁷ The Mixmag survey was led by King's College London.

surveys of drug use show no reported mephedrone use amongst similar groups of young adults surveyed in bars and clubs in 2004-8 (Measham and Moore, 2009).

4.15. Data from the National Poisons Information Service (NPIS) show that telephone inquiries and TOXBASE⁸ accesses relating to cathinones increased sharply over the latter part of 2009 into 2010 (Thomas, 2010). NPIS enquiries more commonly involved males (2:1 sex ratio) and fitted an age profile similar to those taking MDMA with the greater proportion being in the 10-19 and 20-29 age groups, compared to cocaine which has a greater proportion of enquiries concerning the 20-29 and 30-39 age groups.

4.16. The most up to date information regarding visits to the FRANK website relating to the cathinones page are presented in Table 3. The number of visits has more than doubled in the past six months and has shown a month on month increase since September 2009 when the page was first published. This is mirrored by similar increases in calls to the talk to FRANK helpline.

Table 3. Visits to selected pages of the FRANK website⁹ between September 2009 and February 2010*.

	FRANK website visits	Cathinones	% of visits	Cannabis	% of visits	Cocaine	% of visits	Ecstasy	% of visits
Sept-09 (page published 18/09/09)	255,765	9,366	3.7%	58185	22.7%	36925	14.4%	22541	8.8%
Oct-09	376,751	33,167	8.8%	72470	19.2%	47140	12.5%	35745	9.5%
Nov-09	444,069	47,954	10.8%	80246	18.1%	48489	10.9%	33167	7.5%
Dec-09	314,236	54,299	17.3%	53141	16.9%	38570	12.3%	28691	9.1%
Jan-10	358,537	66,236	18.5%	81986	22.9%	53736	15.0%	37910	10.6%
Feb-10	378,576	80,969	21.4%	51319	13.6%	53736	14.2%	38028	10.0%

*percentages are of total visits to individual drug webpages on FRANK website.

4.17. 'Google Insights for search' is a tool that allows search volume patterns, specifically using the Google search engine, to be compared across regions, categories, time frames, and properties. 'Google Insights for search' has been used in this instance to determine the proportion of searches, using Google, to search for the word 'mephedrone' since January 2009 to March 2010 in the UK (England region only)¹⁰. It can be

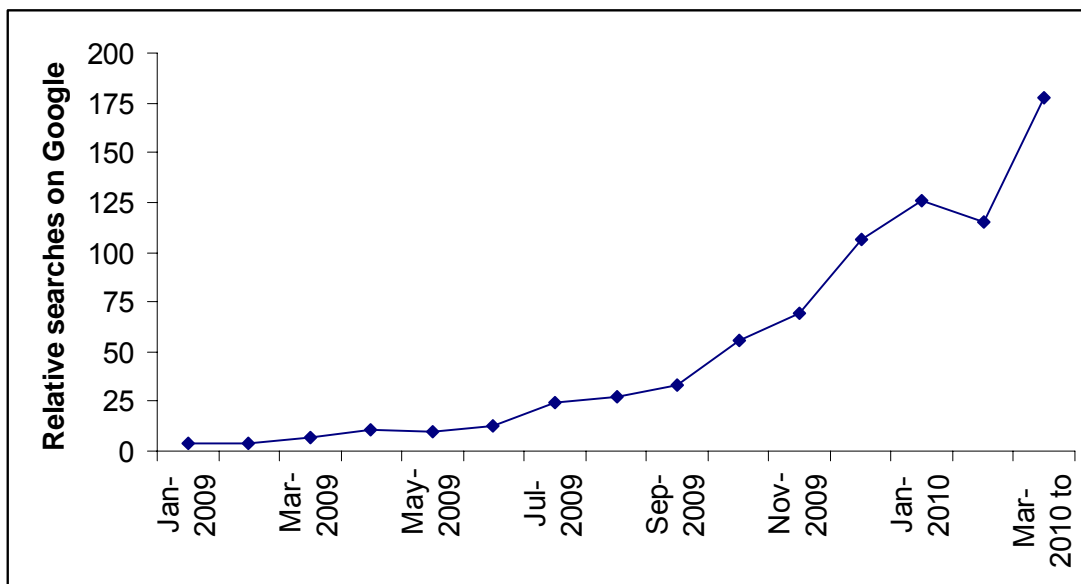
⁸ TOXBASE is the primary clinical toxicology database of the National Poisons Information Service.

⁹ See the following link for FRANK webpage on mephedrone:
<http://www.talktofrank.com/drugs.aspx?id=3597>

¹⁰ The data derived by Google insights does not reflect the actual number of searches carried out on Google. The data actually shows the number of searches for a particular term *relative* to the number of searches done on Google over time. The data is normalised, meaning that it is divided by a common variable to cancel out the effect of that variable on the data. Each point on the graph is divided by the highest point, or 100. When there is not enough data, 0 is shown. For example, if the highest peak is in March, this would be designated as 100. If the

seen from Figure 1 that there is a rising trend in the searches, although the month of March 2010 includes only partial data at this time. Please note that some months overlap due to the way in which the data is collated (weekly rather monthly).

Figure 1. Relative number of searches on Google for the term 'mephedrone'.



4.18. Data provided by the Forensic Science Service (FSS) of police seizures show that the cathinone derivatives account for only a small proportion of total drug seizures. Although the cathinones are not illegal they generally present as 'white powders' (predominantly mephedrone – 89% of cathinone seizures).

next month the searches are half this figure, the second peak would be designated as 50, and so on.

5. Physical harms (toxicity, dependency and mental health)

Acute toxicity

- 5.1. Most data regarding the harms of the cathinones (mephedrone in particular) are self-reported and there are very few clinical data available.
- 5.2. Wood *et al.*, (2009) report the first case of sympathomimetic toxicity related to mephedrone (4-MMC) confirmed by toxicological screening where no other drugs or alcohol were detected.
- 5.3. Data from Guys and St Thomas' hospital toxicology (Dargan and Wood, *pers. comm.*) over the last year show that from a total of 1600-1800 cases, of which 40% are due to recreational drugs, 25 of which presented with toxicity due to self reported mephedrone use (Table 4). Of these 25 cases cases, 80% were male with a mean age of 28.5y (SD \pm 8.0 y). Reported clinical symptoms are shown in Table 5, clinical examination data are shown in Table 6.

Table 4. Cases of toxicity in individuals presenting due to self reported mephedrone use to Guys and St Thomas' hospital

	Number
January – March 2009	2
April – June 2009	0
July – September 2009	8
October – December 2009	5
January 2010 – 22 nd February 2010	10

Table 5. Reported Clinical symptoms for cases of toxicity in individuals presenting due to self reported mephedrone use to Guys and St Thomas' hospital

	% presentations (n=25)
Agitation	52
Palpitations	20
Seizure	12
Vomiting	12
Sweating	12
Headache	4
Discoloration of the skin	0
Cool peripheries	0

Table 6. Clinical examination for cases of toxicity in individuals presenting due to self reported mephedrone use to Guys and St Thomas' hospital

	% presentations (n=25)
Tachycardia >100bpm	48%
Tachycardia >140bpm	16%
Hypertension (>160mmHg)	16%
GCS ≤ 8/15	16%
Bruxism	4%
Hyper-reflexia	4%

5.4. The clinical management of those cases at Guys and St Thomas' was that:

- Four (16%) required benzodiazepines for management of agitation
- Twenty (80%) discharged from ED/observation ward
- Five admitted to hospital
- Four to general medical ward
- One to ICU (for other drug toxicity: GBL)

5.5. Various user reports and clinical observations indicate that mephedrone abuse can cause a number of adverse side effects. Table 7 summarises self reported side effects of mephedrone in terms of increasing severity.

Table 7. Self reported side effects of mephedrone

Modest severity	Moderate severity	Most severe
Reduced appetite	Insomnia	Strong desire to re-dose, craving to recapture initial euphoric rush
Dry mouth	Nausea (27%)*	Uncomfortable changes in body temperature (sweating/chills) (67%)*
Pupil dilation	Trismus and Bruxism	Increased blood pressure and heart rate, palpitations (43%)*
Unusual body sensations	Skin rashes	serious vasoconstriction in extremities, cold or blue fingers (15%*)
Change in body temperature regulation	Nystagmus and dilated pupils Pain and swelling in nose and throat, nose bleeds, sinusitis (when insufflated) Impaired short term memory, poor concentration Dizziness, light headidness, vertigo	high doses can cause hallucinations and psychosis

(51%)*
Headache

*Data from Mixmag survey n=>2,000 (Winstock, 2010)

5.6. When taken in large quantities self-reported experiences by 'psychonaut'¹¹ users described vivid hallucinations during 3 day binges of mephedrone (Linell, 2010). However, the quantities reportedly consumed are not likely to mirror those of most users.

5.7. The ACMD has received anecdotal reports from members of the public that when taken in conjunction with other drugs e.g. amphetamines the effects can be quite marked and lead to personality changes, paranoia and sometimes violent episodes.

5.8. Some of the adverse effects reported for methylone (Table 8) are similar to those reported for MDMA (ecstasy) (ACMD, 2009)

Table 8. Self reported side effects of methylone

Modest to moderate severity	Most severe
Increase in heart rate and blood pressure	Insomnia
General change in consciousness (as with most psychoactives)	Hyperthermia and sweating
Pupil dilation, can lead to blurred vision	Dizziness, confusion
Difficulty in focusing, restlessness	Depersonalization, hallucinations, paranoia, fear (with high doses)
Change in perception of time	Unwanted life-changing spiritual experiences
Slight increase in body temperature	Gastrointestinal discomfort, nausea and vomiting
Muscle tension and aching	Skin rashes common
Trismus and bruxism	Hangover may include exhaustion, depression, disorientation, headache, amnesia.

5.9. It is notable that several commonly reported side effects reflect the sympathomimetic actions of the cathinones. The NPIS is another important, independent source of information collected from telephone enquiries made by health professionals managing people presenting after mephedrone exposure and website visits. The most commonly reported clinical effects included tachycardia, palpitations, agitation, anxiety, palpitations and mydriasis. Chest pain, breathlessness, nausea, vomiting, headache, hypertension, confusion, hallucinations, peripheral vasoconstriction and convulsions have also been reported in some cases (Thomas, 2010). It is notable how closely the NPIS data match those provided from other sources.

¹¹ A person who explores his own psyche, especially by taking psychedelic drugs.

5.10. Data from clinical examination confirms that tachycardia is a common symptom of mephedrone ingestion. Severe cases of cardiovascular toxicity or conditions such as hypopyrexia due to use of cathinones have not been reported (Dargan and Wood, *pers. comm.*). The majority of presentations have been recent and during the winter months, it is not known if the number of presentations due to conditions such as hypopyrexia will change during warmer weather.

5.11. Users also report severe vasoconstriction of extremities, leading to bluing of fingers or hands. It is worth noting that hyperpyrexia and vascular collapse are among the most dangerous life-threatening side effects of amphetamine misuse¹². Some of the acute adverse side effects induced by methylamphetamine include (ACMD, 2005):

- Insomnia
- Increased physical activity
- Decreased appetite
- Increased respiration
- Hyperthermia
- Increased heart rate and blood pressure
- Irregular heart beat
- Cardiovascular collapse and death (in overdose)
- Confusion
- Anxiety
- Tremors

Cases of death where cathinones have been implicated¹³

5.12. There have been at least 18 deaths in England where cathinones have been implicated. Currently, seven of these have provided positive results for the presence of mephedrone at post mortem. To date, in one case the coroner concluded that the death was “natural” and that an inquest was not required. The remaining cases are awaiting inquest.

5.13. There have been at least seven deaths in Scotland where cathinones have been suspected. Of these, one has been confirmed as the result of the “adverse effects of methadone and mephedrone”. Another case is probable, but underlying health issues contributed to the death and it awaits formal confirmation by the relevant Procurator Fiscal. The presence of mephedrone has been confirmed in a third case.

¹² see ACMD Reports on Methylamphetamine, and MDMA - <http://drugs.homeoffice.gov.uk/drugs-laws/acmd/reports-research/index.html>

¹³ Data from the UK has been compiled by John Corkery on behalf of the National Programme on Substance Abuse Deaths from the following sources: Forensic Toxicology Service at St George’s, University of London; Forensic Science Service; Other Forensic Toxicology laboratories; Scottish Crime & Drug Enforcement Agency; Coroner’s offices; Drug & Alcohol Action Teams. In addition, some case details have been derived from media reports. Data is accurate at 26/03/2010.

- 5.14. One case on Guernsey has provided positive post mortem toxicology results for mephedrone and is awaiting inquest.
- 5.15. One suspected case in Wales and a further case in Northern Ireland are awaiting toxicology and inquest.
- 5.16. The UK number of cases are subject to several caveats:
- Not all suspected cases may have been identified;
 - That mephedrone may have been involved in a death cannot be confirmed until the relevant coroner or Procurator Fiscal has concluded her/his inquest or other formal inquiry; and,
 - The presence of mephedrone in post mortem toxicology does not necessarily imply that it caused or contributed to a death.
- 5.17. Mephedrone has been linked to the death of an 18-year old girl in Sweden (Gustaffsson and Escher, 2009). The report (December 2008) indicates that she had taken mephedrone and smoked cannabis. The woman was observed to first become sick and then unconscious. Forensic autopsy showed severe brain swelling, preceded by respiratory and circulatory arrest. No other sedatives, narcotics or alcohol were detected in the blood.

Chronic toxicity

- 5.18. There are so far no reports of the potential harmful effects of the long term use of mephedrone and related cathinones because the substances have only been used in recent months in the UK.

Dependence

- 5.19. Reports from a case study of mephedrone use (Linell, 2010) suggest that users can become regular users rapidly, although they are generally not in a 'state of dependency'. However, this conclusion contrasts with the same report whereby users knew people who became daily users. Some users have reported developing cravings for mephedrone, methylone and MDPV after use. Arguing again by analogy with amphetamines, it is clear that the chronic use of amphetamines can lead to dependence, and a downward cycle of bingeing and periods of recovery associated with depression (ACMD, 2005), therefore it is likely that mephedrone use carries a similar risk of dependency.
- 5.20. Dargan and Wood (2010) report a single case of dependency on mephedrone in Glasgow where the individual had been using the drug for 18 months.
- 5.21. Data are not available on the number of individuals in treatment services related to the cathinones. However, the evidence suggests that the number is likely to be very small at the time of writing.

6. Societal harms

Prevalence

6.1. The current prevalence of mephedrone and the related cathinones is not accurately known. Reports from drugs agencies, drug researchers, criminal justice, public health (Talk to FRANK) and education professionals suggest that mephedrone use appears to be very widespread and is growing. From emergence to current levels of usage, commentators have suggested that the rise in mephedrone use is unprecedented. Namely within a year it has risen from a very low baseline to become popular amongst adolescents and adults.

Young people

6.2. Media reports from the 8th March indicate that secondary school children were missing classes due to the use of the drug mephedrone causing sickness. The DCSF minister of State for Schools and Learners has written to schools. In the letter it makes clear that they *do* have the power to confiscate inappropriate items including a substance that they believe to be mephedrone (or any other drug, whatever its legal status); in line with the school's behaviour policy and that such items do not need to be returned.

6.3. Mephedrone is sold by online retailers for an average price of £10/g. Given that users take approximately one gram over the course of a session, this makes the drug relatively cheap compared with other intoxicants, as well as being more easily available than alcohol and cigarettes for under 18 year olds who have access to the internet or a high street 'head shop'.

6.4. There is some evidence that use has escalated following media reports. For example, Google Trends (which collates Google searches) shows that UK Google searches have increased from a very low base in the last twelve months (see paragraph 4.17), with peaks which coincide with media coverage of mephedrone use and deaths where mephedrone might be implicated. The most popular Google search term is for the words "buy mephedrone online", with four of the top five search terms containing the words "buy" and "mephedrone". Furthermore online mephedrone retailers have reported an increase in sales following media coverage (The Guardian, 2009)

Anti-social behaviour / acquisitive crime

6.5. The ACMD has been presented with two recent cases where mephedrone users have reported that their use was funded by acquisitive crime (robbery and burglary). At present there remains only limited evidence of a relationship between mephedrone and anti-social behaviour; mainly related to the open dealing and consumption of mephedrone. Notwithstanding the legal implications, the dealing in unspecified white powders for the purposes of intoxication can amount to a public nuisance with a detrimental impact on public confidence.

Organised crime

6.6. There are indications that criminal groups are becoming involved in the supply of mephedrone to the public in the UK (SOCA, 2010). At present the mephedrone retail trade operates mainly through internet importation and distribution and 'head shops'. However, there are reports of some UK drug suppliers selling mephedrone in dance clubs and at street level either as well as, or instead of cocaine and MDMA, due to mephedrone's relatively low price, high purity and easy availability. Reports from Guernsey, where importation is currently banned (and prices are reported to be considerably higher), suggest that a street trade in mephedrone has developed. Reports from Guernsey customs officials note that supply is through illegal drug suppliers and incidences of violence have emerged associated with the street trade in mephedrone (McVean, 2010).

Stockpiling

6.7. It is reported that some users are planning to buy large quantities of mephedrone to 'stockpile' for future use and future sale should regulation be introduced (Measham *et al.*, 2010; ACPO, *pers. comm.*). This could lead to an illegal supply of mephedrone coming on to the market should it be controlled under the Misuse of Drugs Act 1971.

Consumption patterns

6.8. It is of concern that there are reports that users of mephedrone have a tendency to re-dose (or 'fiending') and for some individuals the consumption of mephedrone is alone at home (Newcombe, 2010; Linnell, 2010). Together these two features of mephedrone consumption patterns may expose users to increased risks such as overdose or cardiovascular problems.

7. Current controls

Present UK controls

- 7.1. Cathinone (Class C), methcathinone (Class B), diethylpropion (Class C) and pyrovalerone (Class C) are controlled under the Misuse of Drugs Act 1971. However, other derivatives and analogues are not presently controlled (including mephedrone).
- 7.2. Although paragraph 1(c) of Part 1 (Schedule 2) of the Misuse of Drugs Act 1971 offers some scope for the control of substances which are structurally related to the phenethylamine backbone, it is primarily concerned with ring-substituted amphetamine-like compounds. Specifically, no mention is made of the presence of any substituents (other than hydrogen) at the β -carbon of the phenethylamine backbone (recall that the cathinones all possess a β -ketone oxygen; see Figure 1).
- 7.3. Irrespective of whether controls for the cathinones are implemented under the Misuse of Drugs Act 1971, the rapidity and easy availability of mephedrone and other cathinones (including websites set up so that vendors that can deliver to individual addresses) does raise the question of whether other legislation and regulation should be available.

International Control

- 7.4. Some of the substituted cathinones could conceivably be considered as being 'structurally similar' to cathinone and methcathinone, which are both already listed in Schedule 1 of the United Nations Convention on Psychotropic Substances 1971. It is therefore possible that some cathinones could be controlled through the implementation of analogue control where such control mechanisms exist.
- 7.5. Denmark controls a number of cathinones, including mephedrone, methylone and MDPV. Mephedrone has been controlled in Sweden since December 2008; the Swedish authorities have indicated that they also intend to classify MDPV and butylone. Mephedrone is controlled (as a medicinal product) in Finland, and it is anticipated that it will shortly be controlled in Germany, since the German Federal Cabinet made a decision to subordinate a number of materials to the Betäubungsmittelgesetz in January 2009. Methylone is also controlled in the Netherlands.

8. Public Health

- 8.1. The FRANK campaign (see also paragraph 4.16) provides information on the potential risks of taking cathinone compounds and there was also a recent campaign to highlight the dangers of 'legal highs' ('Crazy Chemist').
- 8.2. Lifeline have produced an information leaflet¹⁴ that provides harm reduction advice specific to mephedrone and answers frequently asked questions from users or potential users (Lifeline, 2010). The ACMD is also aware that CairScotland have produced and distributed information leaflets warning of the dangers of these substances (CairScotland, 2010).
- 8.3. Other than the above there is presently a limited amount of public health information regarding mephedrone and the cathinones. Although recent media profile has presented much apparent public health information it is not always credible or consistent.

¹⁴ The publication is available at: <http://lifelinepublications.org/catalogue/methedrone-faqs>

9. Conclusions and recommendations

- 9.1. Although the current prevalence of mephedrone and related cathinones is relatively low in the UK, use appears to have grown rapidly in the past year.
- 9.2. The ACMD would like to emphasise that mephedrone and the related cathinones *are* likely to be harmful to users and in tandem with control mechanisms there should be a credible and comprehensive public health campaign. The messages promulgated by FRANK provide a good basis upon which this should be built.

Control and regulation

- 9.3. The ACMD consider that the harms associated with mephedrone and the cathinones are commensurate with the amphetamines and therefore those substances in Class B; therefore the ACMD recommend that the cathinones be controlled as Class B substances under the Misuse of Drugs Act 1971.
- 9.4. The ACMD recommend that, excluding the four compounds already controlled (see paragraph 2.2) and the API Bupropion, the cathinones should be controlled by a generic definition under the Misuse of Drugs Act 1971 – see Annex A, p31, and in schedule 1 of the Misuse of Drugs Regulations 2001.
- 9.5. The naphthyl analogue of pyrovalerone is now advertised on the Internet and is being retailed as “NRG-1”. The ACMD intend to review these substances and provide further advice at a later date.
- 9.6. The ACMD recommend that the government implement appropriate additional controls and regulation of the cathinones (which would include mephedrone) through, for example:
- Import controls
 - Serious Organised Crime Agency (SOCA)¹⁵
- 9.7. The ACMD understand that to implement import controls is not administratively burdensome and would stop non-EU imports; where it is understood much of the imported cathinones originate from. The ACMD also believe that SOCA have a role in informing suppliers of the cathinones of the implementation of import controls, trading standards and, if implemented, forthcoming control under the Misuse of Drugs Act 1971.
- 9.8. The ACMD notes that the cathinones have no efficacy as plant fertiliser products or as bath salts and could be the subject of a prosecution under the Trade Descriptions legislation.

¹⁵ The involvement of SOCA is most relevant whilst the compounds are still licit.

Public Health

- 9.9. Directors of public health in PCTs should be tasked with cascading information to raise awareness of the cathinones - symptoms of use and information on where to seek advice - among GP's, A&E departments, medical directors / advisors and others as appropriate.
- 9.10. The ACMD recommends that all agencies involved in the health, education and rehabilitation of young persons should disseminate information, in appropriate formats, as provided by the Department of Health and Home Office, as to the risks of using mephedrone (and associated compounds). We include in this Drug Action Teams (and equivalents e.g. DAATs in the Devolved Administrations), Childrens' Trust Boards, Youth Offending Teams and Schools.
- 9.11. We recommend that the FRANK webpages related to the cathinones are given due prominence and that supplementary educational material is easily available. The information provided should be credible and consistent.
- 9.12. In relation to 9.9-9.11 it is important that the risks of mixing these drugs with other substances (including alcohol) are highlighted.
- 9.13. The ACMD are presently identifying information streams to update ministers and provide information on both emerging drugs of misuse and emerging trends concerning established illegal drugs. The ACMD consider that this work will assist it in advising on 'legal highs' in the future. Among other measures, the continuing development of datasets from drug amnesty bins will contribute to providing an early warning of such emerging trends.
- 9.14. Appropriate treatment advice and provision should be available to those who have developed cathinones-related problems of which health professionals and drugs service providers should be aware.

Research

- 9.15. Present forensic analytical testing of the cathinones is expensive and a process that can take some time. Currently, there is no simple drug field test available for cathinones. There is an urgent need to develop a simple and reliable field test.
- 9.16. For the purposes of identification of cathinone derivatives by forensic providers and pathology laboratories, and the development of drug field tests, there is an urgent need to develop and make available a library of reference standards.
- 9.17. There is presently a lack of data concerning the involvement of the cathinones in drug-related deaths (DRDs). Therefore, we recommend that

the Ministry of Justice approach Her Majesty's Coroners to include, in the case of suspected DRDs, tests for the cathinones.

- 9.18. The ACMD welcome the collation of a joint report initiated by the European Drug Centre for Drugs and Drug Addiction (EMCDDA) in respect of mephedrone. However, we understand that this review will be limited in scope to mephedrone as an individual compound. The purpose of the present report is to review the broad spectrum of cathinone derivatives already encountered in the UK and to provide advice to ministers at the earliest opportunity. The ACMD will keep under consideration all emerging evidence including the EMCDDA's forthcoming report(s) and will provide further advice to ministers accordingly.
- 9.19. There is a need for more basic research to examine the similarities and differences between the cathinones and their amphetamine equivalents.
- 9.20. We welcome the inclusion of a specific question on mephedrone in the British Crime Survey to develop the knowledge base on prevalence. The ACMD also recommends more social research to inform our understanding of drug trends, motivations for drug use, fluctuations in demand, and policy implications regarding deterrence, displacement and desistance.
- 9.21. The ACMD would welcome the continuing collation of data sets concerning toxicity, clinical case reports and dependence liability collected from hospital admissions and treatment services.

10. References (including written and oral evidence)

ACMD, 2009. MDMA ('ecstasy'): a review of its harms and classification under the Misuse of Drugs Act 1971. ISBN 978-1-84726-868-6

ACMD, 2005. Methylamphetamine Review.

CairScotland, 2010. Report to the ACMD.

Cozzi, N.V., Sievert, M.K., Shulgin, A.T., Jacobill, P. and Ruoho, A.E. (1999) Inhibition of plasma membrane monoamine transporters by beta-ketoamphetamines. *European Journal of Pharmacology*. **381**: 63-69.

Dal Cason, T.A., Young, R and Glennon R.A. (1997) Cathinone: an investigation of several N-alkyl and methylenedioxy substituted analogs. *Pharmacology Biochemistry and Behavior*. **58**: 1109-1120

Druglink March/April 2009. Mephedrone: The future of drug dealing?

Druglink. January/February 2010. Teenage Kicks. Vol 25. Issue 1.

Druglink. January/February 2010. World Wired Web Vol 25. Issue 1.

Feyissa, A.M. and Kelly, J.P. (2008) A review of the neuropharmacological properties of khat. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. **32**: 1147-1166.

Glennon, R.A., Yousif, M., Naiman, N. and Kaliz, P. (1987) Methcathinone: a new and potent amphetamine-like agent. *Pharmacology Biochemistry and Behavior*. **26**: 547-551.

The Guardian, (2009), Mephedrone and the problem with 'legal highs', 5th December. Online at:
<http://www.guardian.co.uk/society/2009/dec/05/mephedrone-problem-legal-highs> [accessed 30th March 2010]

Gustaffsson, D. and Escher, C. (2009) Mefedron. Internetdrog som tycks ha kommit för att stanna. (Mephedrone - Internet drug that seems to have come to stay). *Läkartidningen*. **106**: 2769-2771.

Hand, T., Rishiraj, A. (2009) Seizures of Drugs in England and Wales 2008/09. Home Office Statistical Bulletin 16/09. London: Home Office.

Lifeline. 2010. *Mephedrone Frequently Asked Questions*.
www.lifelinepublications.org (publications@lifeline.org.uk)

Linell, M. (2010) Case study: use of mephedrone in a Northern Town. The Lifeline project. Oral evidence to the ACMD.

- McVean, C. (2009) The adverse effects of those “Legal High” powders containing cathinone derivatives on the community in Guernsey. States of Gurnsey, Customs and Immigration Service.
- McVean, C. (2010) The impact of cathinones on a small island community. States of Gurnsey, Customs and Immigration Service.
- Measham, F. and Moore, K. (2009) Repertoires of Distinction: Exploring patterns of weekend polydrug use within local leisure scenes across the English night time economy; *Criminology and Criminal Justice*, **9**: 437-464.
- Measham, F., Moore, K., Newcombe, R. and Welch, Z. (2010) Tweaking, bombing, dabbing and stockpiling: the emergence of mephedrone and the perversity of prohibition. *Drugs and Alcohol Today*. **10**: 14-21.
- Meltzer, P.C., Butler, D., Deschamps, J.R. and Madras, B.K. (2006) (4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogues: a promising class of monoamine uptake inhibitors. *Journal of Medicinal Chemistry*. **49**: 1420-1432.
- Nagai, F., Nonaka, R. and Kamimura, K.S.H. (2007) The effects of non-medically used drugs on monoamine neurotransmission in rat brain. *European Journal of Pharmacology*. **559**: 132-137.
- Newcombe, R. (2010) *Mephedrone: the use of mephedrone (m-cat, Meow) in Middlesbrough*. Manchester: Lifeline Publications & Research.
- New Musical Express* (2010), Mephedrone – How dangerous is the UK’s favourite new drug, 8th February. Online at: <http://www.nme.com/blog/index.php?blog=10&p=7956&more=1> [accessed 30th March 2010]
- Ramsey, J. (2010) Analysis of white powders seized by UK border agency at London Heathrow airport. Written evidence to the ACMD.
- Serious Organised Crime Agency (SOCA). (2010) Drugs report – Mephedrone.
- Sumnall, H. and Wooding, O. (2009) Mephedrone – an update on current knowledge. North West Public Health Observatory, Centre for Public Health, Liverpool John Moores University.
- Thomas, S. (2010) Enquiries relating to the cathinones. National Poisons Information Service, Health Protection Agency. Oral evidence to the ACMD.
- UK Border Agency (2010) UKBA – Treatment of cathinones at the frontier. Written evidence to the ACMD.

White, M. (2010) Cathinone Derivatives: Chemistry, Prevalence and Legal status. Forensic Science Service. Oral evidence to the ACMD.

Winstock, A. (2010) Results of the 2009/10 Mixmag drug survey. Oral evidence to the ACMD.

World Health Organisation (1995) WHO Expert Committee on Drug Dependence. Twenty-ninth report. WHO Technical Report Series. No.856.

Wood, D.M., Davies, S., Puchnarewicz, M., Button, J., Archer, R., Ramsey, J., Lee, T., Holt, DW. and Dargan, P.I. (2009) Recreational Use of 4-methylmethcathinone (4-MMC) presenting with sympathomimetic toxicity and confirmed by toxicological screening. *Clinical Toxicology*. **47**: 733.

Zaitso, K., Katagi, M., Kamata, H., Kamata, T., Shima, N., Miki, A., Tsuchihashi, H. and Mori, Y. (2009) Determination of the metabolites of the new designer drugs bk-MBDB and bk-MDEA in human urine. *Forensic Science International*. **188**: 131-139.

Annex A. Recommendation for the generic control of the cathinone derivatives

Scope of a generic definition

The ACMD here set out recommendations on the range of compounds that should be included in a generic definition for the control of cathinone derivatives under the Misuse of Drugs Act 1971.

It was proposed that the scope of compounds covered by generic control should be much wider than the 6 ring substituted compounds listed in Table 1 (annex A) and wider than the 10 compounds reported to the EMCDDA since 2006.

The scope should include all cathinone derivatives that have been found in seizures and collected samples together with compounds that have not been encountered but have misuse potential. This includes cathinone derivatives with and without ring substituents and with side chains longer than those usually encountered in the phenethylamine drugs.

The scope should also include any substances known or believed to be pro-drugs, i.e. substances that are metabolised to a known active substance (for example GBL is converted in the body to GHB).

The generic definition should not include those substances already controlled under the Misuse of Drugs Act, i.e. diethylpropion (Class C), cathinone (Class C), methcathinone (Class B) and pyrovalerone (Class C). Finally the definition should not include any substances, e.g. bupropion, that are ingredients of legitimate pharmaceutical products or that have other legitimate uses.

The structure of cathinone derivatives is represented by the generalised structure below:

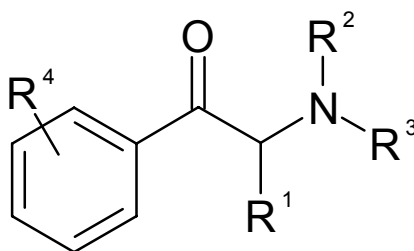


Figure 1: Generalised structure of cathinone derivatives

where,

R¹ = single alkyl group [but not H]

R² = H or alkyl

R³ = H or alkyl or

[NR²R³] = pyrrolidino or phthalimido or other ring structure

R⁴ = H (no substituents) or

= one or more of alkyl, alkoxy, alkylendioxy and halide whether or not further substituted with an other univalent substituent

The phthalimido group has so far only been encountered in the compound α -phthalimidopropiophenone. This substance has been found in a capsule in combination with 2-fluoromethcathinone and in capsules containing a mixture with 4-methylmethcathinone, *N*-ethylcathinone, and caffeine.

The reason for adding α -phthalimidopropiophenone is not clear. It may have been added deliberately, perhaps as a pro-drug for cathinone, but there is no information about its pharmacology or metabolism. This substance is also an intermediate in the synthesis of cathinone and *N*-alkyl derivatives of cathinone. It could therefore be present unintentionally as a residue of an intermediate, the product of a failed chemical synthesis, or even the mislabelling of an intermediate.

In addition to compounds with the generalised structure in (Figure 1, Annex A) the phenyl ring can be replaced with a naphthyl ring (e.g. Figure 2, Annex A) or with a thiophene ring. The naphthyl analogue of pyrovalerone (Figure 2, Annex A) is available on the Internet and is being retailed as “NRG-1”. These compounds cannot easily be included in a generic definition for the cathinone derivatives having the generalised structure in Figure 1, Annex A, but they could be controlled as named substances or by one or more separate generic definitions. The ACMD intend to review these substances and provide further advice at a later date.

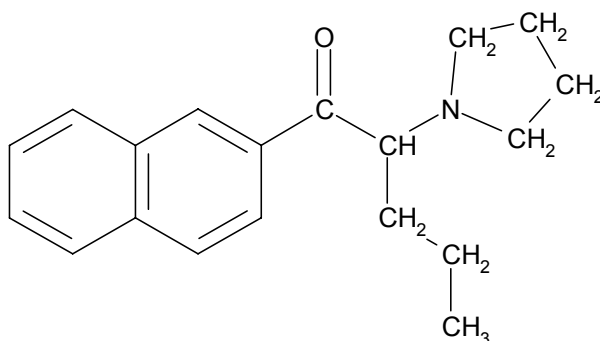


Figure 2: Naphthyl analogue of pyrovalerone

The systematic chemical name for the structure in Figure 2, Annex A is 1-(2-naphthyl)-2-(1-pyrrolidinyl)-1-pentanone and alternative names include naphthylpyrovalerone, naphyrone and O-2482.

Appendix I, of this Annex includes all the cathinone derivatives, with the general structure in Figure 1, Annex A, that have been encountered in seizures and collected samples, substances that are already controlled, ingredients of known pharmaceutical products, substances available via the Internet and substances that are listed in Wikipedia. However, the market for cathinone derivatives is still evolving and new substances will continue to appear.

Many cathinone derivatives are mentioned in patents for pharmaceutical applications but the only known non-controlled cathinone derivative with a marketing authorisation appears to be bupropion, an ingredient of ®Zyban.

Some cathinone derivatives are mentioned in patents for non-pharmaceutical applications.

A structure-based search of the 12th Edition of the Merck Index (1996), carried out previously by Dr Les King, found no contentious compounds.

Interestingly, a recent patent (WO PCT 2010006196) relating to water purification membranes mentions the compound in Figure 3 below, which is closely related to methyldone (bk-MDMA). This compound would be included within a generic definition since the term methylenedioxy can have two meanings. However, compounds analogous to those in Figure 3, Annex A are unlikely to have any commercial uses.

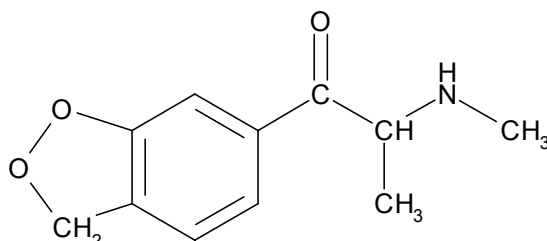


Figure 3: 3,4-methylenedioxy-N-methyl- β -keto-amphetamine

Structure Activity Relationships

Cathinone derivatives have a range of effects (e.g. stimulant, empathogen and antidepressant).

The cathinone derivatives without ring substituents (e.g. diethylpropion, methcathinone, buphedrone, N,N-dimethylcathinone) are mostly stimulants.

Most of the cathinone derivatives encountered as legal highs are ring substituted compounds with a secondary amino group (R^2 = methyl or ethyl and R^3 = hydrogen) or with a cyclic amino group (NR^2R^3 = pyrrolidino group or phthalimido group). These substances are primarily stimulants, with varying degrees of empathogenic effects (i.e. similar in effects to MDMA). Ring substituents (R^4) have included alkyl, alkoxy, methylenedioxy and halide.

The side chain substituent (R^1) has mostly been a single alkyl group. However there are examples with allyl (an alkenyl) and propargyl (an alkynyl) groups and also examples with a second alkyl group attached to the same carbon atom as R^1 , but these compounds are not within the proposed scope.

No haloalkyl substituents (e.g. trifluoromethyl $-CF_3$ as found in piperazine derivatives) in the ring (R^4) or on the side chain (R^1) have been encountered or reported in the literature. However, replacement of the ring methyl group, as in mephedrone, with a trifluoromethyl group is likely to produce substances with similar activities. It is recommended therefore that haloalkyl substituents be included in the generic definition for ring substituents.

Cathinone derivatives with a primary amino group (i.e. no N-alkyl substituents) are rarely encountered, possibly because of their instability. There are only two known examples, bk-MDA (known to substitute for MDMA in rats) and cathinone (a stimulant).

The NR^2R^3 amino groups reported in the scientific literature have included alkylamino ($R^2 = \text{alkyl}$, $R^3 = \text{H}$), dialkylamino ($R^2 = \text{alkyl}$, $R^3 = \text{alkyl}$), the cyclic pyrrolidino group and a large number of other cyclic amines. However, for the pyrovalerone analogues an increase in size of the nitrogen containing ring from a five-membered pyrrolidine ring to a six-membered piperidine ring resulted in a substantial loss in binding potency. There are also examples of N-allyl, N-propargyl and N-cycloalkyl substituents.

The anti-depressant drug bupropion has a *tertiary*-butyl group on the nitrogen atom and several other substances investigated for their potential as smoking cessation drugs also have a bulky alkyl group on the nitrogen atom, e.g. *tertiary*-butyl, *iso*-propyl or cycloalkyl, or the alkyl amino group is replaced by a cyclic piperidino group (a cyclic amino group with 6 membered ring).

Salts, stereoisomers, esters and ethers

Cathinone derivatives with the generalised structure in Figure 1, Annex A, all have an asymmetric α -carbon atom giving rise to R and S stereoisomers.

With the exception of the phthalimido derivatives, all cathinone derivatives have a basic nitrogen atom and can therefore form salts.

There is no definition of esters and ethers in the Misuse of Drugs Act 1971, but from a chemical perspective esters usually only applies to derivatives of acids with a hydroxyl group, and derivatives of alcohols and phenols. Likewise ethers usually only applies to derivatives of alcohols and phenols. On this basis the cathinone derivatives would not form esters or ethers.

However, keto compounds, $R^1R^2C=O$, can form ketals, $R^1R^2C(OR')_2$, which arguably might be described as a special form of an ether. Ketals of cathinone derivatives have been discussed on drug forums in the context of a pro-drug and are mentioned in the scientific literature, usually as a means of protecting the keto group during chemical syntheses.

Generic definition for the control of cathinone derivatives

The ACMD have considered a number of options for the control of cathinone derivatives, including listing of named substances, several generic definitions and combinations of these approaches.

Taking into account the ACMD's consideration of the scope, together with structure activity relationships and prevalence of known cathinone derivatives, the following generic definition is recommended:

Any compound (not being bupropion or a substance for the time being specified in paragraph 2.2) structurally derived from 2-amino-1-phenyl-1-propanone by modification in any of the following ways, that is to say,

- (i) by substitution in the phenyl ring to any extent with alkyl, alkoxy, alkylendioxy, haloalkyl or halide substituents, whether or not further substituted in the phenyl ring by one or more other univalent substituents;*
- (ii) by substitution at the 3-position with an alkyl substituent;*
- (iii) by substitution at the nitrogen atom with alkyl or dialkyl groups, or by inclusion of the nitrogen atom in a cyclic structure.*

Notes

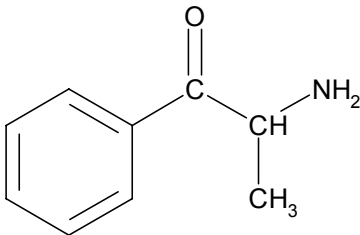
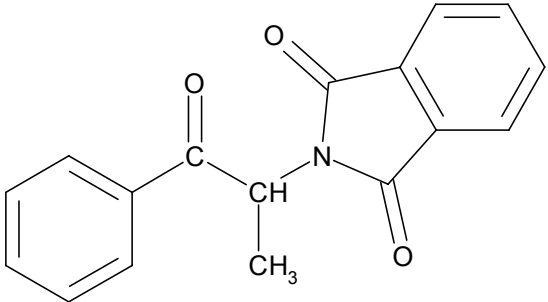
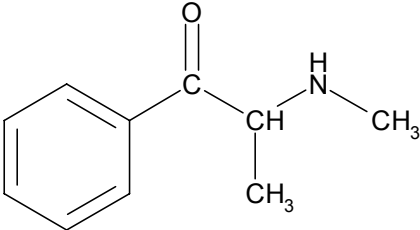
- *the parent compound is cathinone*
- *“any” is taken to mean one or more*

Comments

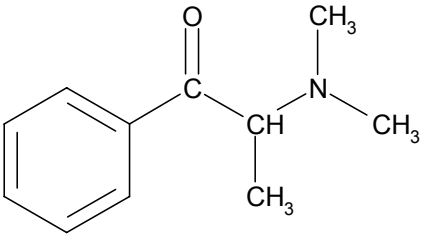
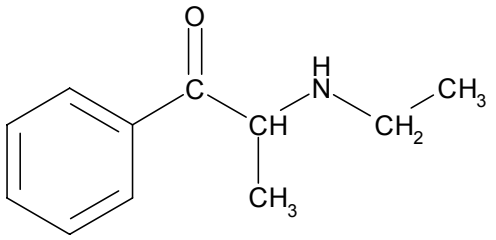
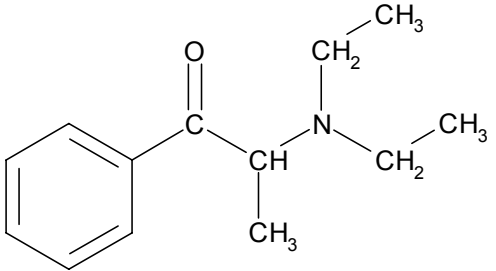
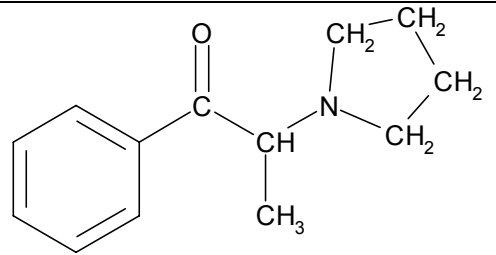
This is a definition that includes all permutations for the three substitution areas, i.e. in the ring (R^4), in the side chain (R^1) and on the nitrogen (NR^2R^3).

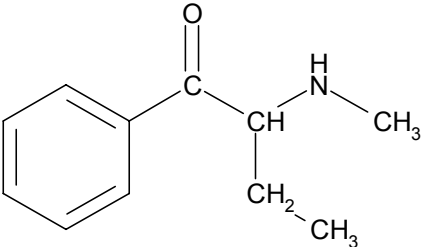
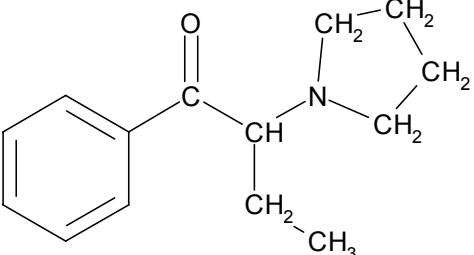
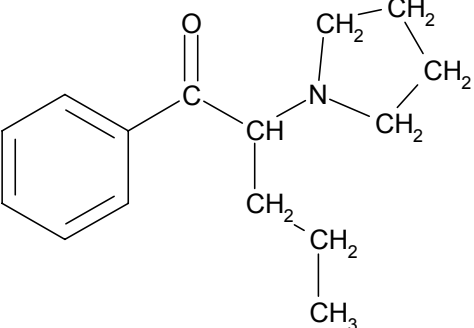
- All the cathinone derivatives would be in the same Class which would result in some anomalies for compounds already controlled.
- Includes all the compounds in Appendix 1.
- Includes primary amines without ring substituents (no known examples, except cathinone which is not included within the scope of this definition).
- Includes ring substituted primary amines (bk-MDA is the only example).
- The term “*cyclic structure*” has a very wide scope (e.g. all ring sizes, all heterocyclic nitrogen compounds and structures with ring substituents).

Appendix 1

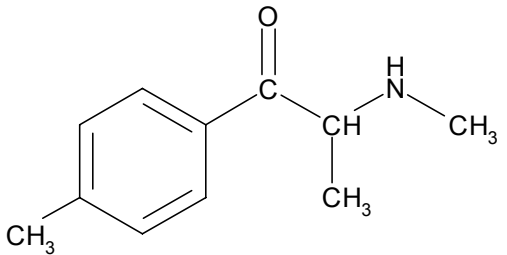
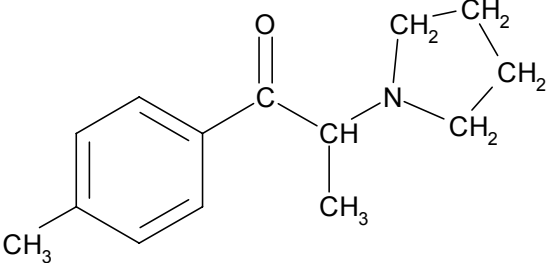
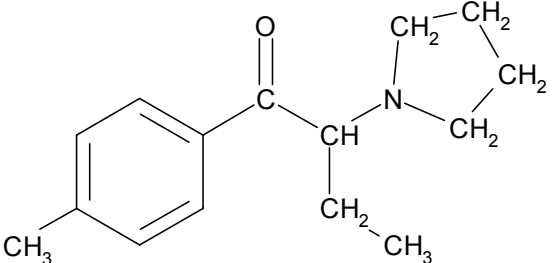
Names	R ¹	R ²	R ³	R ⁴	Structure
Cathinone (Class C) beta-keto-amphetamine <u>Note:</u> only encountered in Khat although it has been encountered as the pro-drug, α -phthalimidopropiophenone (see below)	Me	H	H	H	
α -phthalimidopropiophenone <u>Note:</u> found in products from the Internet	Me	NR ² R ³ = phthalimide		H	
Methcathinone (Class B) Ephedrone α -methylaminopropiophenone	Me	Me	H	H	

Cathinones report – DRAFT – V6

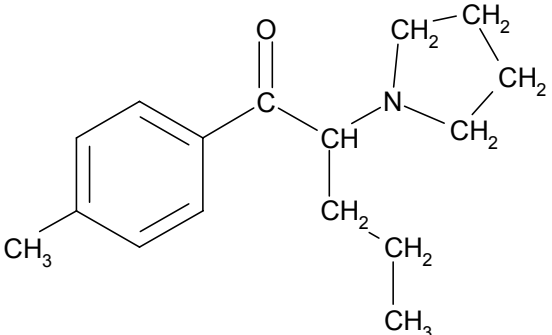
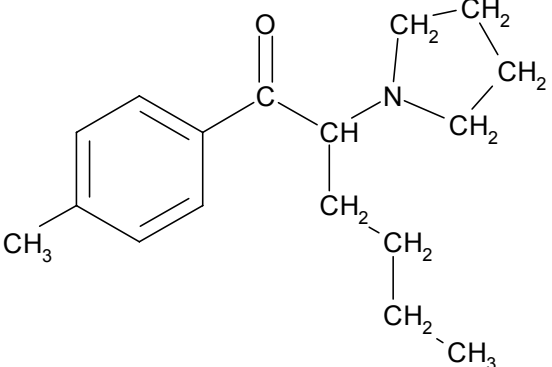
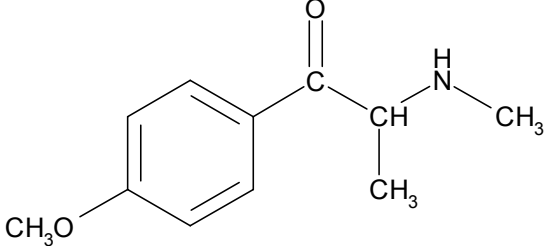
Names	R ¹	R ²	R ³	R ⁴	Structure
<i>N,N</i> -Dimethylcathinone Metamfepramone Dimethylpropion <u>Note</u> : encountered in seizures	Me	Me	Me	H	
Ethcathinone Ethylpropion <i>N</i> -ethylcathinone 2-ethylamino-propiofenone Sub Coca II <u>Note</u> : encountered in seizures	Me	Et	H	H	
Diethylpropion (Class C) Diethylcathinone Amfepramone	Me	Et	Et	H	
α-Pyrrolidinopropiophenone α-PPP <u>Note</u> : encountered in Germany	Me	NR ² R ³ = Pyrrolidinyl		H	

Names	R ¹	R ²	R ³	R ⁴	Structure
2-methylamino-1-phenylbutan-1-one Buphedrone <u>Note:</u> no seizures reported to EMCDDA but is available via the Internet and user reports are on drug forums.	Et	Me	H	H	
α -Pyrrolidinobutiophenone α -PBP <u>Note:</u> no seizure or user reports but listed on Wikipedia and in a patent	Et	NR ² R ³ = Pyrrolidinyl		H	
α -Pyrrolidinovalerophenone α -PVP α -Pyrrolidinopentiophenone <u>Note:</u> No seizures reported to EMCDDA, but metabolism study by Germany, as a result of 2 seizures, in Germany and Netherlands.	<i>n</i> -Pr	NR ² R ³ = Pyrrolidinyl		H	

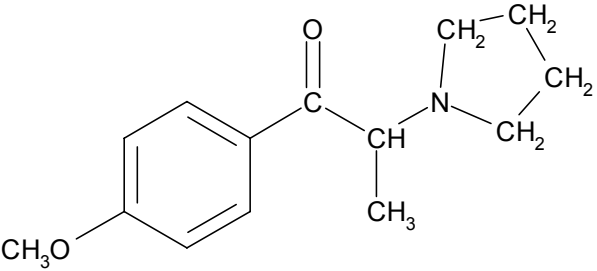
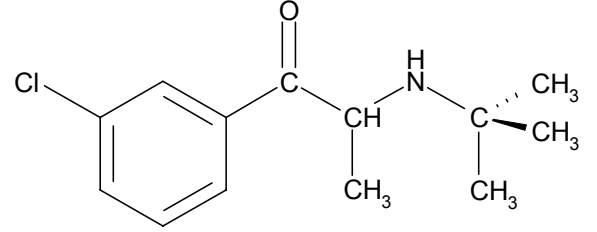
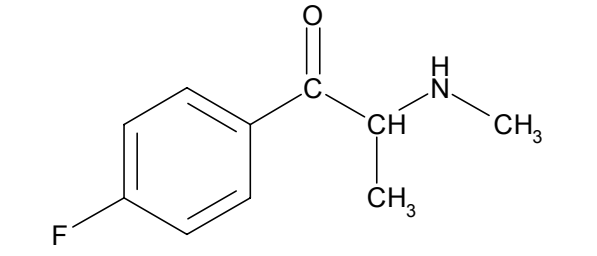
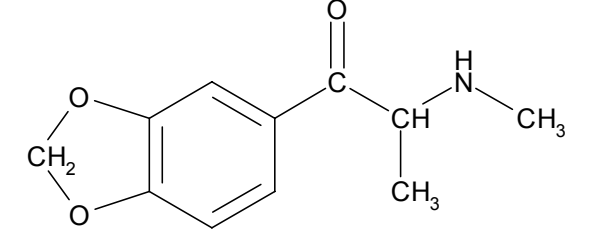
Cathinones report – DRAFT – V6

Names	R ¹	R ²	R ³	R ⁴	Structure
4-Methylmethcathinone 4-MMC Mephedrone Sub Coca I <u>Note</u> : most frequently encountered cathinone derivative	Me	Me	H	4-Me	
4'-methyl- α -pyrrolidinopropiophenone MPPP <u>Note</u> : seizure report from Germany	Me	NR ² R ³ = Pyrrolidinyl		4-Me	
4'-methyl- α -pyrrolidinobutiophenone MPBP <u>Note</u> : seizure report from Germany	Et	NR ² R ³ = Pyrrolidinyl		4-Me	

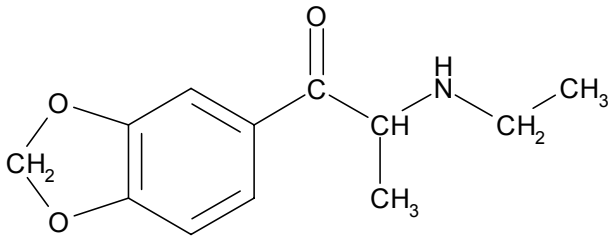
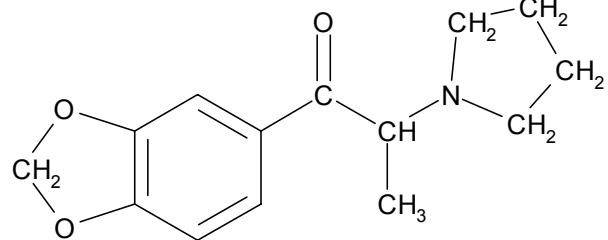
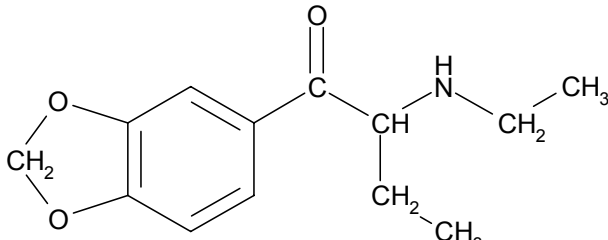
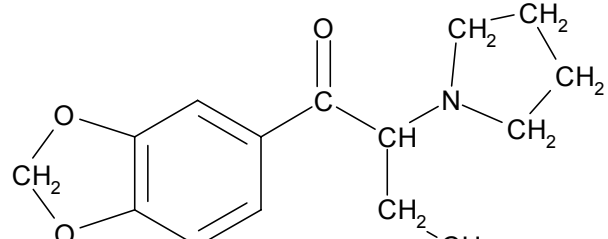
Cathinones report – DRAFT – V6

Names	R ¹	R ²	R ³	R ⁴	Structure
Pyrovalerone (Class C)	<i>n</i> -Pr	NR ² R ³ = Pyrrolidinyl		4-Me	
4'-methyl- α - pyrrolidinohexiophenone MPHP <u>Note:</u> seizure report from Germany	<i>n</i> -Bu	NR ² R ³ = Pyrrolidinyl		4-Me	
4-methoxymethcathinone PMMC Methedrone bk-PMMA <u>Note:</u> encountered in seizures	Me	Me	H	4-MeO	

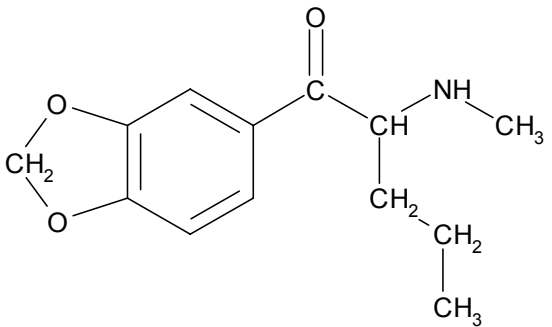
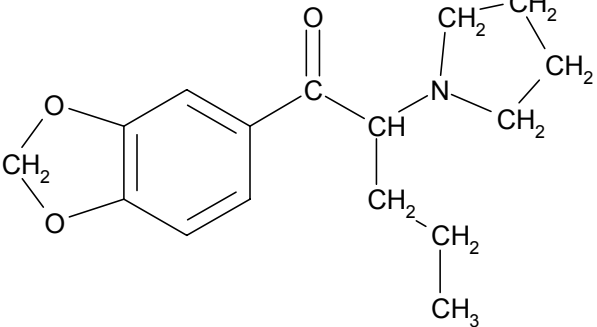
Cathinones report – DRAFT – V6

Names	R ¹	R ²	R ³	R ⁴	Structure
4'-Methoxy- α -pyrrolidinopropiophenone MOPPP <u>Note:</u> seizure report from Germany	Me	NR ² R ³ = Pyrrolidinyl		4-MeO	
Bupropion (Zyban – medicinal product in UK) <u>Note:</u> To be excluded from control. No reports of abuse	Me	<i>t</i> -Bu	H	3-Cl	
4-Fluoromethcathinone Flephedrone 4FMC <u>Note:</u> encountered in seizures. The 3-fluoro and 2-fluoro isomers have also been found in products from the Internet.	Me	Me	H	4-F (also 2-F and 3-F)	
3,4-Methylenedioxy-methcathinone Methylone bk-MDMA <u>Note:</u> encountered in seizures	Me	Me	H	3,4-methylenedioxy	

Cathinones report – DRAFT – V6

Names	R ¹	R ²	R ³	R ⁴	Structure
3,4-methylenedioxyethcathinine Ethylone bk-MDEA <u>Note</u> : encountered in seizures	Me	Et	H	3,4-methylenedioxy	
3',4'-methylenedioxy- α -pyrrolidinopropiophenone MDPPP <u>Note</u> : seizure reports from Germany and Denmark	Me	NR ² R ³ = Pyrrolidinyl		3,4-methylenedioxy	
β -keto-N-methyl-3,4-benzodioxylbutanamine Butylone bk-MDBD <u>Note</u> : seizure reports from 7 countries	Et	Me	H	3,4-methylenedioxy	
3',4'-Methylenedioxy- α -pyrrolidinobutiophenone <u>Note</u> : no seizure reports, but mentioned in Wikipedia and in patent	Et	NR ² R ³ = Pyrrolidinyl		3,4-methylenedioxy	

Cathinones report – DRAFT – V6

Names	R ¹	R ²	R ³	R ⁴	Structure
Pentylone β -Keto- methylbenzodioxolypentanamine bk-Methyl-K bk-MBDP <u>Note:</u> no seizure reports, but mentioned in Wikipedia and in patent	n-Pr	Me	H	3,4-methylenedioxy	
Methylenedioxypropylvalerone MDPV <u>Note:</u> encountered in seizures	n-Pr	NR ² R ³ = Pyrrolidinyl		3,4-methylenedioxy	

Annex B. Members of the Advisory Council on the Misuse of Drugs

Member	Sector
Professor Leslie Iversen (ACMD Chair)	Professor of Pharmacology, Oxford University
Lord Victor Adebowale	Chief Executive, Turning Point
Dr Dima Abdulrahim	Briefings Manager, National Treatment Association
Mrs Gillian Arr-Jones	Chief Pharmacist for the Care Quality Commission
Mr Martin Barnes	Chief Executive, Drugscope
Dr Margaret Birtwistle	Specialist General Practitioner, Senior Tutor – Education and Training Unit, St George’s Hospital and Forensic Medical Examiner
Commander Simon Bray	Commander, Metropolitan Police
Mr Eric Carlin	Former Chief Executive of Mentor
Ms Carmel Clancy	Principal Lecturer for Mental Health and Addiction, Middlesex University
Professor Ilana Crome	Professor of Addiction Psychiatry, Keele University
Ms Robyn Doran	Mental Health Nurse and Director of Operations, North-West London Mental Health Trust
Professor Simon Gibbons	Professor of Phytochemistry (natural product chemistry), School of Pharmacy, University of London
Mr Patrick Hargreaves	Advisor for Drugs and Alcohol, Durham County Council Education Department
Ms Caroline Healy	National Adviser for the commissioning of mental health services for children in secure settings, Department of Health
Dr Matthew Hickman	Reader in Public Health and Epidemiology, Department of Social Medicine, University of Bristol

Dr Fiona Measham	Senior Lecturer in Criminology, University of Lancaster
Mr David Liddell	Director, Scottish Drugs Forum
Mr Hew Mathewson CBE	Dentist and former President and Chair of the General Dental Council (2002 to 2009)
Mr Trevor Pearce	Director of Enforcement, Serious Organised Crime Agency
District Judge Justin Phillips	District Judge, Drugs Court London
Mr Richard Phillips	Independent Consultant, Phoenix Futures
DCC Howard Roberts	Deputy Chief Constable, Nottinghamshire Police
Dr Mary Rowlands	Consultant Psychiatrist in Substance Misuse, Exeter
Ms Monique Tomlinson	Freelance Consultant in Drugs Misuse
Mr Arthur Wing	Assistant Chief Officer – Sussex Probation Area

Annex C. Organisations and affiliated individuals submitting evidence concerning the cathinones to the Advisory Council on the Misuse of Drugs, February 22nd 2010.

Association of Chief Police Officers

Association of Chief Police Officers in Scotland

Avon and Somerset Constabulary Bunt, P

Cair, Scotland Burns, M

Centre for Public Health, Liverpool John Moore's University

Customs & Excise, Immigration and Nationality Service - Guernsey McVean, C

Drugscope

Forensic Science Service White, M

FRANK Department of Health / Home Office

Guernsey customs and Excise McVean, C

Guys and St Thomas' Hospital, London Dargan, P, Wood, D

Isle of Man Department of Home Affairs

Key Forensic

Kings College London Winstock, A

Lancaster University Measham, F

LGC Forensics Treble, R

Lifeline Linell, M

National Poisons Information Service Scientifics Ltd Thomas, S

Serious Organised Crime Agency St Georges University London, National Programme on Substance Abuse Deaths Corkery, J

TICTAC Communications

Ramsey, J

UK Border Agency

Deller, P

Members of the public

The ACMD is very grateful to all those who have submitted evidence and lent their expertise to our understanding of the cathinones.

Annex D. Letter from the Advisory Council on the Misuse of Drugs to the Home Secretary.

ACMD

Advisory Council on the Misuse of Drugs

Secretary: Will Reynolds
3rd Floor (SW), Seacole Building
2 Marsham Street
London
SW1P 4DF
Tel: 020 7035 0454
ACMD@homeoffice.gsi.gov.uk

Rt Hon Alan Johnson
2 Marsham Street
London
SW1P 4DF

22nd December 2009

Dear Home Secretary,

Re: ACMD consideration of mephedrone (and related cathinones)

The ACMD wrote to you in March to explain that it would be pleased to accede to the Government's priorities that your predecessor set out in her letter of 13 March 2009. Concerning the issue of 'legal highs' the ACMD has provided advice on the synthetic cannabinoid receptor agonists (Spice), 1-benzylpiperazine, GBL and 1,4-BD all of which we note will be controlled in the legislation on the 23rd December. In the ACMD's letter of 30 September 2009 it was explained that we would next provide you with advice on the cathinones.

Despite the difficulties of the last 2 months the ACMD is committed to providing you with advice on the cathinones. Although attention has focused on mephedrone, five other synthetic psychoactive cathinone derivatives are also widely available. The ACMD explained in a previous letter to you that it has concerns about the apparent prevalence and potential harms of these compounds. Much has been made of these compounds in the media over recent weeks; we find it of concern that this may have had the consequence of bringing such drugs to the attention of a wider demographic sooner than may have been the case.

The ACMD understand that mephedrone, amongst other cathinones, is being marketed as a variety of apparently 'benign' products e.g. bath salts or plant food. Whilst the potential harms of these drugs are not yet fully known, it is apparent that the selling of such unregulated preparations in a form that they are clearly unintended for could have serious public health implications.

The ACMD is mindful that, after recent events, our statutory membership requirements need to be fulfilled before providing formal advice, according to the requirements of the Misuse of Drugs Act 1971. However, the ACMD would like to assure you that it will seek to provide you with such advice at the earliest possible opportunity on this important issue.

I would be willing to discuss the issue of the cathinones and, more broadly, new psychoactive substances ('legal highs') and the timing of advice with you.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Les Iversen'. The signature is written in a cursive style with a large initial 'L'.

**Professor Les Iversen
(on behalf of the ACMD)**