

ACMD

Advisory Council on the Misuse of Drugs

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Rt Hon. Theresa May MP

Home Office

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18th October 2012

Dear Home Secretary,

In March 2012 the ACMD advised that methoxetamine be subject to a temporary class drug order. Methoxetamine was marketed as a legal alternative to ketamine until a temporary class drug order was implemented in April 2012. As is now required, the ACMD has followed its initial assessment with a consideration of methoxetamine in the context of the Misuse of Drugs Act 1971; I enclose the report with this letter.

The chemical structure of methoxetamine bears a close resemblance to that of both ketamine and phencyclidine (PCP, 'Angel Dust', a class A drug), which both produce well-documented and serious adverse effects following both acute and chronic usage.


Users report that the effects of methoxetamine are similar to those of ketamine, however, some users report that the effects are of longer duration. The harmful effects reported include severe dissociation, cardiovascular symptoms, paranoid thoughts and unpleasant hallucinations.

The first analytically confirmed series reported by Guy's and St Thomas' NHS Foundation Trust, London in 2011, was of three individuals who presented having self-reported use of methoxetamine. All three presented with a ketamine-like dissociative state, but also had significant stimulant effects with agitation and cardiovascular effects including tachycardia and hypertension. Toxicological screening of serum samples confirmed methoxetamine use in two of the cases. A subsequent analytically confirmed case series has shown that methoxetamine also causes significant acute cerebellar toxicity.

The ACMD has reviewed the harms of methoxetamine and finds a broadly similar picture of physical harms to that presented in its last report..

The ACMD considers, from the available evidence, that the harms of methoxetamine are commensurate with Class B, of the Misuse of Drugs Act (1971); and it should be scheduled under Schedule I of the Misuse of Drugs Regulations (2001) (having no known recognised medicinal use). The ACMD also recommend that a number of closely related analogues of ketamine and phencyclidine, some of which have already appeared on sale as 'legal high alternatives', be controlled by means of a generic chemical description detailed in Annex 3.

Yours sincerely,

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

Professor Les Iversen

Cc :

Minister of State for Crime Prevention

Parliamentary Under Secretary of State for Public Health

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1. Pharmacology

- 1.1 Methoxetamine is an analogue of ketamine. Pharmacologically, ketamine's main action is on glutamate, the major excitatory neurotransmitter in the brain. It is a non-competitive antagonist at one of the three glutamate receptor subtypes, the *N*-methyl D-aspartate (NMDA) receptor (Morgan and Curran, 2011). The NMDA receptor is also considered to be a key pharmacological target for phencyclidine (Gorelick and Balster, 1995; Bey and Patel, 2007). Although there is little information available on the novel ketamine and PCP analogues, their behavioural effects in human subjects resemble those induced by ketamine and PCP, being characteristic of dissociative anaesthetics (Corazza *et al*, 2012). The wanted effects include euphoria, empathy, dissociation from the physical body, hallucinations, but these may be accompanied by adverse side effects, which include dizziness, confusion, psychomotor agitation, and cognitive impairment. The clinically reported symptoms of acute toxicology of methoxetamine include a 'dissociative catatonic' state similar to that seen with ketamine use, accompanied by sympathomimetic toxicity, with significant tachycardia and hypertension (Wood *et al.*, 2011; Hofer *et al.*, 2012). Reversible cerebellar toxicity has also been reported in three cases of acute methoxetamine toxicity (Shields *et al.*, 2012). A major physical harm associated with chronic ketamine use is bladder and renal tract toxicity leading, in particular, to severe ulcerative cystitis which can cause bladder dysfunction (Morgan and Curran 2011, Kalsi *et al.*, 2011). Chronic ketamine use can also be associated with dependence and a number of other chronic complications including abnormal liver function tests, and of neuropsychiatric disorders (Kalsi SS 2011). It is not known whether methoxetamine will also prove to be associated with these chronic effects.
- 1.2 The resources of the National Institute of Mental Health "Psychoactive Drug Screening Program" were used to obtain neurochemical profiles of methoxetamine and some of the novel PCP analogues and to compare these with those of ketamine and PCP and other reference compounds. The results confirmed that methoxetamine and the other novel analogues have significant affinity for glutamate NMDA receptors, and reveal the possibility of other effects mediated by monoamine transporter targets and sigma receptors. Interaction with the glutamate NMD receptor is thought to be the key factor underlying the mechanism of action of ketamine, phencyclidine and other dissociative anaesthetics.

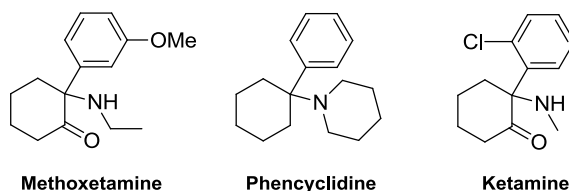
*Binding Assays*¹

- 1.3 Results of binding assays are given in annex 1.

¹ K_i determinations, receptor binding profiles were provided by the National Institute of Mental Health's Psychoactive Drug Screening Program (PDSP), Contract # HHSN-271-2008-00025-C (NIMH PDSP). The NIMH PDSP is directed by Bryan L. Roth MD, PhD at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscoll at NIMH, Bethesda MD, USA.

2. Chemistry

- 2.1 Methoxetamine (2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone) is one of a group of compounds collectively referred to as the arylcyclohexylamines. Other compounds of this type have applications as anaesthetics and some have been used as recreational drugs. Perhaps the best known arylcyclohexylamines are phencyclidine (1-(1-phenylcyclohexyl)piperidine, 'PCP', 'Angel dust') and ketamine (2-(2-chlorophenyl)-2-(methylamino)cyclohexanone, 'Special K').



- 2.2 PCP and some related materials (Eticyclidine, Rolicyclidine, Tenocyclidine) are controlled as Class A drugs (see Annex 2 for structures).
- 2.3 Synthesis of methoxetamine is achievable by 4 steps through simple reactions involving an aromatic nitrile, a Grignard reagent, bromination, imine formation through reaction with a suitable amine, followed by the application of heat to the product to allow ring expansion (Hays et al., 2012). This process is presumably readily applicable to analogues of methoxetamine by substitution of starting aromatic nitrile and selected amine to afford the desired *N*-substituted derivative analogues of methoxetamine.
- 2.4 Ketamine, a human and veterinary pharmaceutical which became popular as a recreational drug, was made a Class C drug in 2005. Methoxetamine was subsequently advertised, by legal high suppliers, as a legal alternative to ketamine, that is, as a 'designer drug'.
- 2.4 'Legal high' websites are currently offering other novel uncontrolled psychoactive substances - arylcyclohexylamines - including 3-methoxy and 4-methoxy PCP, and these were also found to interact with high affinity at the NMDA receptor (see Annex 2).
- 2.5 2-Methoxy ketamine, another arylcyclohexylamine (table 2) closely related to methoxetamine and ketamine, has recently been announced by several websites as a new product and on 30th August 2012 the EMCDDA reported that the Swedish Police had made the first seizure of this variant of ketamine in Europe.
- 2.6 In early September 2012, a further new compound of this type, *N*-ethyl-nor-ketamine ('NEK', Annex 2) was made available on a number of websites. Its identity was confirmed by an EMCDDA notification issued on 17th September, 2012. This material is a homologue of ketamine, that is, it has a chemical structure identical to ketamine, except that the *N*-methyl group is replaced by an *N*-ethyl group, so the compound can be expected to have effects that are substantially similar to those of ketamine.

3. Harms

Acute Harm

- 3.1 There have been six published cases of analytically confirmed acute methoxetamine toxicity presenting to hospitals in the UK (Wood, 2012, Shields, 2012). In addition to the analytically confirmed cases from London and York, there is anecdotal information on presentations to hospitals in other areas of the UK including Scotland, the Midlands and the South West.
- 3.2 Analysis of NPIS data collected up to the end of July 2012 demonstrates that there have been 47 telephone enquiries to the UK National Poisons Information Service (NPIS) concerning cases of suspected methoxetamine exposure or toxicity; the first of these was in October 2010. In addition there have been 298 user sessions to the monograph for methoxetamine on TOXBASE, the online poisons information database for the NPIS from the date of its publication in May 2011 until 31st July 2012.
- 3.3 The most common clinical features reported in telephone enquiries to NPIS following methoxetamine exposure were agitation and tachycardia. Hypertension, confusion, dizziness, euphoria, somnolence, catatonia or hypertonia and elevated creatine kinase were also documented commonly (>8% cases).
- 3.4 Data from NPIS needs to be interpreted with caution as the National Poisons Information Service usage can only give surrogate information on presentations to hospital with toxicity and case numbers are limited. However these data suggest increasing presentations to hospitals related to the use of methoxetamine, particularly since November 2011. Telephone enquiry and TOXBASE session numbers have fallen since April 2012, suggesting a possible association with the temporary class order on the availability and prevalence of use of methoxetamine that came into effect on 5th April 2012.
- 3.5 The first analytically confirmed series reported by Guy's and St Thomas' NHS Foundation Trust, London in 2011, was of 3 individuals who presented having used methoxetamine. All three presented with a ketamine-like dissociative state but also had significant cardiovascular stimulant effects: tachycardia (113–135 bpm) and hypertension (systolic BP 187–201 mm Hg, diastolic BP 78-104mmHg). Toxicological screening of serum samples confirmed methoxetamine use (serum methoxetamine concentrations 0.09–0.2 mg/L) and this was the only detected substance in 2 of the cases (Wood, 2012).
- 3.6 The second analytically confirmed series was of 3 individuals in York who presented with mild stimulant cardiovascular features (HR 67–107 bpm, systolic BP 148–194 mmHg, diastolic BP 104–112 mm Hg). In addition all of them had significant cerebellar signs (truncal ataxia [unsteadiness on their feet], nystagmus and incoordination) that persisted for up to 3-4 days. Toxicological screening of serum samples confirmed methoxetamine use (0.24-0.45 mg/L), and no other drugs were identified on an extended toxicological screen (Shield, 2012).
- 3.7 In summary, methoxetamine appears to be associated with some features that are similar to ketamine (hallucinations, drowsiness, and dissociative effects). Ketamine can cause mild hypertension, however the hypertension reported in methoxetamine toxicity is greater than what would generally be expected with ketamine toxicity. In

addition to more significant hypertension, methoxetamine appears to be associated with additional toxicity compared to ketamine including agitation, other stimulant effects such as tachycardia (a fast heart rate) and cerebellar features. Cerebellar features such as ataxia (unsteadiness on the feet), are rarely seen with other recreational drugs and are not seen with acute ketamine toxicity.

Chronic Harm

- 3.8 Regular use of ketamine is associated with a range of chronic problems including bladder and other lower urinary tract pathology (Kalsi SS *et al.*, 2011).
- 3.9 Methoxetamine is frequently marketed as “bladder friendly”, however preliminary data from animal studies show that it is associated with significant bladder and kidney toxicity (Wood DM *et al.*, Clin Toxicol (Phila) 2012). There is currently no data to determine how this compares to the effects seen with ketamine in the same animal models.
- 3.10 There are currently no reported human cases of methoxetamine related bladder toxicity, however it has only been available / used for 1-2 years and therefore it is possible that it is too early for these effects to have been reported.
- 3.11 Regular use of ketamine is also associated with other chronic toxicity including gall bladder, gastrointestinal and central nervous system damage. There is currently no published animal or human data to determine whether methoxetamine has similar effects.

Deaths

- 3.12 The ACMD is not aware of any deaths solely attributed to methoxetamine.

Crime

- 3.13 Methoxetamine was openly offered for sale on UK websites prior to the temporary ban. Implementation of the ban had a real and immediate impact in tackling internet sales of methoxetamine with a significant proportion of UK websites ceasing to advertise its sale. It is possible that methoxetamine remains available online but sold under other descriptions. However, the extent of such availability and of methoxetamine's prevalence in the market place is unclear. Since the temporary ban, seizures of Methoxetamine in the Metropolis have been low, spread over a broad area with no obvious hot spots. It does not seem to be a drug of choice; it is not particularly prevalent and is not a crime generator.

International data

- 3.14 The ACMD are not aware of any confirmed deaths solely related to methoxetamine reported in Europe or elsewhere in the world.
- 3.15 There has been one published case of potential acute methoxetamine toxicity from Switzerland and one from the USA. These cases are summarised below.
- 3.16 The US case was an individual who presented to the Emergency Department after self-reported methoxetamine use in a dissociative state. In addition he had mild stimulant features (HR 105 bpm, BP 140/95 mm Hg) and bilateral nystagmus (abnormal eye movements). Analysis of a drug specimen suggested that the drug used was methoxetamine, however it is not possible to determine definitively whether

toxicity was due to methoxetamine as there was no toxicological screening of biological samples to confirm actual use of methoxetamine (Ward J 2011).

- 3.17 The case from Switzerland was an individual who reported injection of methoxetamine. On arrival in the Emergency Department, he was agitated, had ataxia, and was disoriented. He also had stimulant features (HR 134 bpm, BP 168/77 mm Hg) and a mild pyrexia (37.6°C). However, this individual had also injected MDMA (3,4-methylenedioxymethamphetamine) 2 days previously. Analysis of serum samples taken 5 hours after injection of methoxetamine showed both methoxetamine and MDMA and therefore it is not possible to determine the relative role of these drugs in the presentation (Hofer KE 2012).
- 3.18 In addition there are anecdotal reports of acute methoxetamine toxicity presentations to hospitals in other countries in Europe including in Belgium.

Treatment services

- 3.19 FRANK and Know the Score provide general information about methoxetamine and its current legal status. Information provided focuses on dissociative effects of methoxetamine, and both sites list some adverse effects that it is claimed are not seen with ketamine (involuntary eye movement, loss of balance and poor coordination, gait instability and slurred speech). However, it is unclear what the source of this claim is. The two sites also suggests that methoxetamine is/was being marketed as a 'bladder safe' replacement for ketamine, but again, the source of this statement, and relevance in light of the temporary class drug order (TCDO), is uncertain. As ketamine is injected by some users (it is unknown whether this is also true for methoxetamine), general information is provided on the risks of methoxetamine injection, and how sharing of equipment may lead to increased risk of transmission of blood borne viruses. DAN (Wales) does not currently provide any methoxetamine information on its website.
- 3.20 Several other internet sites provide information on methoxetamine, that upon initial inspection seem reliable. For example, the Vaults of Erowid methoxetamine pages provide a more comprehensive overview than FRANK, with the inclusion of links to some scientific studies and user reports. The Independent Scientific Committee on Drugs includes similar information to FRANK but also provides general harm reduction advice. Crew 2000 (www.crew2000.org.uk; a drug service based in Edinburgh) have published a methoxetamine briefing targeted at users and drug workers which includes information on dose and user patterns, harm reduction, and weblinks.

4. Prevalence of use and price

- 4.1 There is only a small amount of evidence of methoxetamine use in the UK, and this is largely confined to nightlife populations; this does not, however, mean that the prevalence of use is low. As methoxetamine is not included in the Crime Survey for England and Wales (CSEW; formerly British Crime Survey) it is unclear to what extent methoxetamine had dispersed amongst the general population and whether geographic variations in use exist. There is currently no evidence available on user typology and so it is not possible to predict which groups are most likely to use methoxetamine. Surveys have been conducted which have indicated some use amongst gay male 'clubbers' and young adult 'clubbers' and music festival attendees. However, this is because these populations have been specifically targeted for research.
- 4.2 There are three small prevalence studies to date, and to the best of ACMD's knowledge no other studies are in preparation. The prevalence data reported below is largely the same as reported in the ACMD's earlier report on methoxetamine which was prepared in order to inform the temporary class drug order recommendation and therefore figures do not reflect the apparent reduction in availability of methoxetamine. In the absence of robust epidemiological data it is unknown if the introduction of the TCDO affected methoxetamine prevalence.
- 4.3 It is not possible to provide a UK estimate of methoxetamine prevalence. For comparison purposes, ketamine was reportedly used by 0.6% of the adult population (16-59 years old) in the previous year (2011/12 CSEW data); 1.8% of 16-24 year olds reported use in the same reporting period, a decrease from 2.1% in 2010/11.
- 4.4 A survey has been conducted across four nights in two South London gay dance clubs in July 2011, 6.4% of respondents (82% men, mean age 29.7) reported lifetime use of methoxetamine, 1.9% in the previous month, and 1.6% on the night of survey (Wood *et al*, 2012). For comparison, 76% reported a lifetime use of cocaine, 69 % ecstasy and 64% mephedrone. The lifetime prevalence of other 'Novel Psychoactive Substances' (NPS) was low (e.g. MDAI 7.7%), which led the authors to conclude that of these category of drugs, only mephedrone has become established in nightlife.
- 4.5 A survey by Welch and colleagues (2012) undertaken in Lancashire nightclubs in March 2012 found low levels of methoxetamine use. Customers at these nightclubs would be expected to be more representative of the general public than those frequenting dance clubs, given that these were 'mainstream' nightclubs that were selected at random from all late licensed dancing venues in the fieldwork area. Whilst no-one reported either having already taken or planning to take methoxetamine on the fieldwork night, 3.6% reported having tried it at least once in their lifetime, 2.6% within the last year (March 2011-12) and 1.9% within the last month.
- 4.6 An online survey of self-selected and self-reported substance use conducted November 2011 (Global Drug Survey²) found, of the 7,700 respondents in the UK, 4.2% reported using methoxetamine in the previous year (6% of clubbers and 4% of non clubbers) and 2.4% reported using methoxetamine in the previous month (3% of

² Data available from <https://docs.google.com/spreadsheets/ccc?key=0AonYZs4MzIZbdDdrY2NMeWZpQzZwekxUU19TdWVrc3c#gid=0>

clubbers and 1% of non clubbers). Self reported methoxetamine use amongst this group was higher than the use of a range of other drugs including: DMT; synthetic cannabinoids; Benzofury; MDAI; crack; GBL; BZP; heroin etc.

- 4.7 The same survey reported that 14.4% of last year methoxetamine users would like to use less methoxetamine, and 1% would like to stop. The reasons for reduction/cessation weren't provided.
- 4.8 Anecdotal evidence obtained from drug user forums suggests that some users combine methoxetamine with other compounds, including some tryptamine and phenethylamine derivatives (Corazza *et al.*, 2012), although the veracity of this information is uncertain.
- 4.9 Recent studies conducted in the Westminster and Soho area of central London have detected methoxetamine in urinals indicating that it is being used amongst individuals frequenting the night time economy in these areas (Archer J *et al.*, 2012)

Police exercise to measure prevalence of methoxetamine

- 4.10 The ACMD notes that Avon and Somerset Constabulary undertook an exercise to measure the prevalence of methoxetamine across England and Wales from a policing perspective. The following actions undertaken;
- All Police Forces in England and Wales were contacted for their methoxetamine seizure data over the last 12 months (it is noted that the TCDO only came into force in April 2012).
 - The three main Forensic providers contacted for their methoxetamine seizure data for 2012.
- 4.11 In total 36 replies from Police Forces in England and Wales were received, of these, 14 Forces state that they had made a total of 49 seizures of methoxetamine. 29 of these seizures occurred in the South of England (Kent to the South West) and the rest evenly spread across the Midlands, North England and Wales. It is noted that even when a drug is identified by their Forensic provider many Police Forces do not list that drug in their returns unless it has a Home Office code - this may explain the disparity between Police and Forensic providers figures below.
- 4.12 The number of methoxetamine seizures supplied to the Forensic providers by Police during 2012 was:
- ESG (Environmental Scientific Group) – 75
 - LGC (LGC Forensics) – 171
 - KEY (Key Forensic Services Limited) – 3
- 4.13 In June 2012 Police reports to the ACMD indicated that methoxetamine was not considered prevalent in any Police Force in England and Wales. Some of the Forces that were seizing the drug stated that many of their seizures were as a result of action against "Legal High shops". That view does not appear to have changed.

Methoxetamine price

4.14 Before being subject to a TCDO, and dependent upon the retailer, methoxetamine was available for purchase online for around £5-10 for 250mg, and >£3500 for 1kg (manufacturer prices unknown). As of 30/8/12 five purported UK based sellers were offering methoxetamine for sale on the Silk Road website (an 'anonymous' marketplace accessed using the Tor 'hidden service' browser). Prices ranged from 1.82 Bitcoins (1 Bitcoin [B] ~£7 at the time of writing) for 500mg to 104.24 B for 50g. Sellers purportedly based in China and the USA were offering the opportunity to purchase 1kg of methoxetamine for around 500 B. This indicates a trade outside of those normal routes of access and purchase. According to some drug services street prices are currently around £15-20/g.

Methoxetamine identified by FEWS at Music Festivals across the UK in 2012

4.15 In the summer of 2012, the Home Office Forensic Early Warning System (FEWS) installed and ran on-site drugs laboratories at six music festivals across the UK. The aim of this was to (i) provide intelligence data to the Police regarding the drugs being encountered at the festivals and (ii) to gather information on new psychoactive substances (NPS) for FEWS. Packets and wraps containing a range of powders, capsules and herbal products were collected from drug amnesty bins, police arrests and welfare tents.

4.16 All the samples were tested using either colorimetric and immunoassay kits and then analysed by Gas Chromatography – Mass Spectrometry (GC-MS). The identifications were based on MS library matches together with GC retention times in some cases. Methoxetamine was encountered in both tablet and powder form in 20 of the 1091 samples which were analysed. It was a single component in some samples and found in combination with other drugs which are controlled under the Misuse of Drugs Act, 1971; uncontrolled NPS and cutting agents.

- Six powder samples were identified as methoxetamine only.
- Five powder samples were mixtures in which methoxetamine was combined with
 - i. mephedrone;
 - ii. lidocaine, 4-methyl buphedrone, caffeine, 5-MeO-DALT, cocaine and MDAI;
 - iii. TFMPP, caffeine, MDAI, cocaine and 5-MeO-DALT;
 - iv. 5-MeO-DALT, methylone and 5/6-APB and
 - v. 5-MeO-DALT, methylone, 5/6-APB and 2-DPMP.
- At three of the festivals, methoxetamine was identified nine times in tablets which also contained
 - i. MDMA, n-ethylbuphedrone, 4-MEC and caffeine.

All the samples containing methoxetamine were either in clear poly-bags or wraps and were never seen in a branded product.

5. Conclusions and Recommendations

- 5.1 The ACMD notes that although the number of seizures nationally is relatively low at approximately 270 in 2012 so far, it is clear that methoxetamine is a popular drug especially amongst ketamine users. Notwithstanding the low seizure figures it would appear to be available across the whole of England and Wales, considering its Temporary Class Drug status, methoxetamine has been found in “Legal High” samples seized by Police. There is also evidence that suggests that users refer to methoxetamine as the “bladder safe” ketamine which, with ketamine’s increasing popularity in mind, may lead to an increase in the use of methoxetamine.
- 5.2 Methoxetamine appears to be associated with some features that are similar to ketamine (hallucinations, drowsiness, and dissociative effects). The hypertension reported in methoxetamine toxicity is greater than what would generally be expected with ketamine toxicity. In addition to more significant hypertension, methoxetamine appears to be associated with additional toxicity compared to ketamine including agitation, other stimulant effects such as tachycardia (a fast heart rate) and cerebellar features. Cerebellar features such as ataxia (unsteadiness on the feet), are rarely seen with other recreational drugs and are not seen with acute ketamine toxicity.
- 5.3 Regular use of ketamine is associated with a range of chronic problems including chronic bladder and other lower urinary tract pathology. Methoxetamine is frequently marketed as “bladder friendly”, however preliminary data from animal studies show that it is associated with significant bladder and kidney toxicity (Wood, 2012).
- 5.4 It is recommended that the harms of methoxetamine and the various other analogues of ketamine and phencyclidine, described in 5.2 and 5.3 above (compounds described in the generic scope), are commensurate with other Class B compounds. Therefore the ACMD recommends that methoxetamine and compounds in the generic scope below be brought under the Misuse of Drugs Act 1971 as Class B compounds and be placed in Schedule 1 of the Misuse of Drugs Regulations (2001) as amended.
- 5.5. The ACMD, in its report ‘*consideration of the Novel Psychoactive (‘legal highs’)*’ provided a number of cross-cutting recommendations in relation to public health, treatments and availability. The ACMD believes that these recommendations are relevant to methoxetamine, and should be re-visited by the relevant Departments in order to consider harm reductions measures in relation to methoxetamine.

Annex 1. Results of binding assays of methoxetamine

Compounds were initially screened in quadruplicate primary assays at a fixed concentration of 10 μ M. Those which yielded inhibition of tracer binding of more than 50% at this concentration were subjected to Secondary assays in which test substance concentrations ranging from 10pM to 10 μ M were tested in triplicate to yield concentration effect curves from which pK_i and K_i values were calculated. For experimental details refer to the PDSP web site <http://pdsp.med.unc.edu/> and click on "Binding Assay" or "Functional Assay" on the menu bar. All compounds were screened against the targets listed in Table 1 below.

Table 1: Primary and Secondary Radioligand Binding Assays

Serotonin Receptors	5-HT _{1A} , 5-HT _{1B} , 5-HT _{1D} , 5-HT _{1E} , 5-HT _{2A} , 5-HT _{2B} , 5-HT _{2C} , 5-HT ₆ , 5-HT ₇
Dopamine Receptors	D ₁ , D ₂ , D ₃ , D ₄
Glutamate Receptors	NMDA Receptor (MK-801 binding site), mGluR ₅
GABA Receptors	GABA-A, GABA-B
Biogenic Amine Transporters	SERT, NET, DAT
Adrenoceptors	α_{2A} , α_{2B} , α_{2C} , β_1
Muscarinic Receptors	M ₁ , M ₂ , M ₃ , M ₄
Opioid Receptors	MOR, KOR, DOR
Sigma Receptors	Sigma ₁ , Sigma ₂
Histamine Receptors	H ₁ , H ₂

Results

Table 2 summarises the results obtained with compounds that were active in the Primary assays at 10 μ M,

Table 2: Results of Binding assays – pK_i ± SE, (K_i) nM

Open boxes with – indicate that compounds failed the Primary Screen criterion of >50% inhibition at 10µM. All the compounds failed the Primary Screen criterion in the other screening targets listed in Table 1.

Compound	NMDA	SERT	NET	Sigma ₁	Sigma ₂
Ketamine	6.18±0.07 (659)	-	-	-	-
Phencyclidine	7.23±0.07 (59)	5.65±0.05 (2234)	-	-	6.82±0.09 (136)
Methoxetamine	6.59±0.06 (259)	6.32±0.05 (481)	-	-	-
4-MeO-PCP	6.39±0.06 (404)	6.07±0.05 (844)	6.1±0.1 (713)	6.5±0.1 (296)	7.93±0.08 (143)
3-MeO-PCP	7.69±0.08 (20)	6.7±0.1 (216)	-	7.4±0.1 (42)	-

NMDA (N-methyl-D-aspartate receptor); SERT (serotonin transporter); NET (norepinephrine transporter)

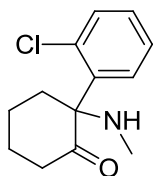
Conclusions from binding data

The results obtained in receptor screening confirm that the novel analogues share the profile of ketamine and PCP as ligands for the glutamate NMDA receptor. The binding data revealed methoxetamine to have an affinity for the NMDA receptor comparable to or higher than the parent compound ketamine. The methoxy analogues of PCP also had appreciable affinities for the NMDA receptor, and 3-MeO-PCP in particular proved particularly active, with a K_i of 20 nM placing it among the most potent known NMDA antagonists (cf dizocilpine (MK-801) K_i = 4.8nM).

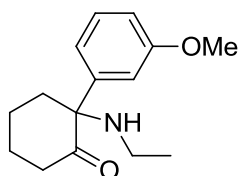
Methoxetamine and the phencyclidine analogues also had appreciable affinity for the serotonin transporter (SERT) (Table 2). The affinity of methoxetamine for SERT was similar

to its affinity for the NMDA receptor, suggesting that inhibition of SERT and a resulting increase in the release of serotonin in the brain may contribute to its psychopharmacological profile and the additional features seen in acute methoxetamine toxicity.

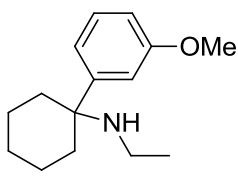
Annex 2. Structure of methoxetamine and closely related compounds – see Annex 4 for those compounds that would be captured by the proposed generic definition (generic description provided at Annex 3).



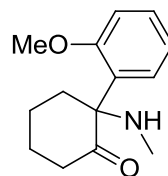
Ketamine



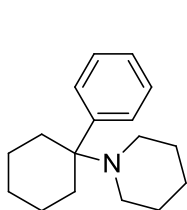
Methoxetamine



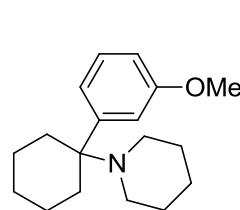
3-MeO-PCE



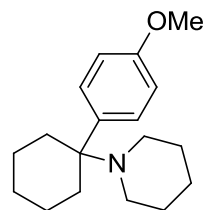
2-Methoxyketamine



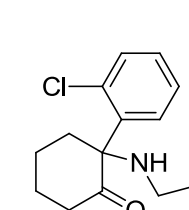
Phencyclidine



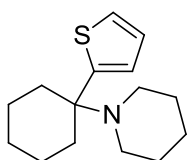
3-MeO-Phencyclidine



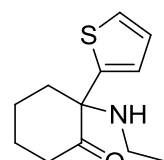
4-MeO-Phencyclidine



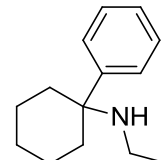
N-ethyl-nor-ketamine



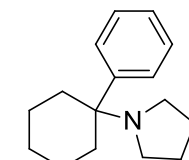
Tenocyclidine



Tiletamine



Eticyclidine



Rolicyclidine

Annex 3. Proposed generic definition.

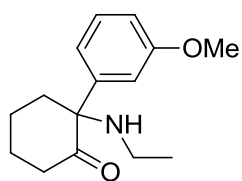
Generic definition of the arylcyclohexylamine dissociative anaesthetics.

1-Phenylcyclohexylamine or any compound (not being ketamine, tiletamine or a compound for the time being specified in paragraph (a) of schedule 1 above) structurally derived from 1-phenylcyclohexylamine or 2-amino-2-phenylcyclohexanone by modification in any of the following ways, that is to say,

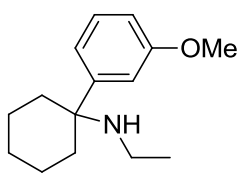
- (i) by substitution at the nitrogen atom to any extent with alkyl, alkenyl or hydroxyalkyl groups, or replacement of the amino group with a 1-piperidyl, 1-pyrrolidyl or 1-azepyl group whether or not the nitrogen containing ring is further substituted with one or more alkyl groups;*
- (ii) by substitution in the phenyl ring to any extent with amino, alkyl, hydroxy, alkoxy or halide substituents, whether or not further substituted in the phenyl ring to any extent;*
- (iii) by substitution in the cyclohexyl or cyclohexanone ring with one or more alkyl substituents;*
- (iv) by replacement of the phenyl ring with a 2-thienyl ring.*

[Note: If Class B is preferred then Schedule 2, Part II, paragraph 2A would need amending ie provisions for esters and ethers since the above generic definition covers those compounds that include an –OH functional group on the phenyl ring].

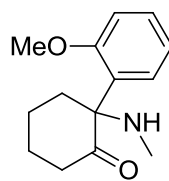
Annex 4. Examples of compounds that would be controlled by the proposed generic



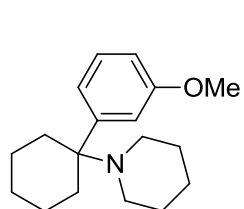
Methoxetamine



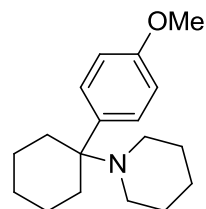
3-MeO-PCE



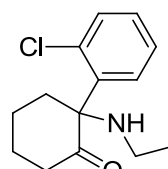
2-Methoxyketamine



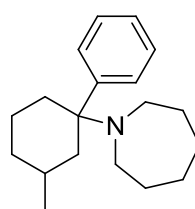
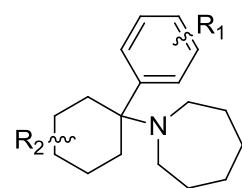
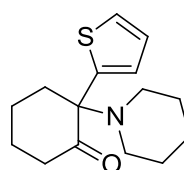
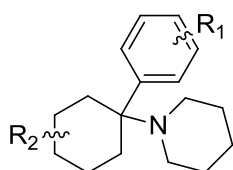
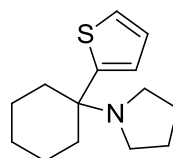
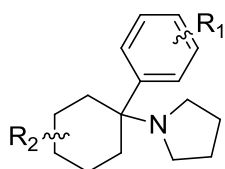
3-MeO-Phencyclidine



4-MeO-Phencyclidine



N-ethyl-nor-ketamine



Where R₁ is amino, alkyl, hydroxy, alkoxy or halide

Where R₂ is alkyl

References

ACMD (2011) Advisory Council on the Misuse of Drugs, "Consideration of the Novel Psychoactive Substances ('Legal Highs')", October 2011

<http://www.homeoffice.gov.uk/publications/agencies-public-bodies/acmd1/acmdnps2011?view=Binary>

ACMD (2012) Advisory Council on the Misuse of Drugs, "Statement of Evidence on Methoxetamine", March 23, 2012 [<http://www.homeoffice.gov.uk/publications/agencies-public-bodies/acmd1/statement-methoxetamine?view=Binary>]

Ahmadi A, Solati J, Kajikhani R and Pakzad S (2011) Synthesis and analgesic effects of new pyrrole derivatives of phencyclidine in mice. *Arzn Forsch*, 61: 296-300.

Archer JRH, Dargan PI, Hudson S, Wood DM. (2012) Using analysis of pooled urine samples from stand-alone urinals (pissoirs) in London to confirm significant use of novel psychoactive substances *Clin Toxicol (Phila)*, 50: 678-679.

Archer JR, Dargan PI, Hudson S, Wood DM. (2012) Analysis of anonymous pooled urine from portable urinals in central London confirms the significant use of novel psychoactive substances. *Q J Med*, *In Press*.

Bey T and Patel A (2007) Phencyclidine intoxication and adverse effects: a clinical and pharmacological review of an illicit drug. *Cal J Emerg Med*, 8: 9-14.

Chaudieu I, Vignon J, Chicheportiche M, Kamenka JM, Trouiller G and Chicheportiche R (1989) Role of the armotic group in the inhibition of phencyclidine binding and dopamine uptake by PCP analogs. *Pharm Biochem Behav*, 32: 699-705.

Carazza O, Schifano F, Simonato P, et al (2012) Phenomenon of new drugs on the Internet: the case of ketamine derivative methoxetamine. *Hum Psychopharmacol Clin Exp*, 27: 145-149.

Casale JF (2011) 4-Methoxyphencyclidine: An Analytical Profile. *Microgram Journal* 8(2): 39-42.

EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) Annual Report 2010 & 2011, [www.emcdda.europa.eu/publications/annual-report-2010] (and 2011)

Gorelick DA and Balster RL (1995) Phencyclidine (PCP) in "Psychopharmacology the Fourth Generation of Progress", New York, Raven Press.

Hays PA, Casale JF, Berrier AL. (2012) The characterization of 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (Methoxetamine) *Microgram Journal*, 9(1), 3-17.

Hofer KE, Grager B, Müller DM, Rauber-Lüthy C, Kupferschmidt H, Rentsch KM, and Ceschi A (2012) Ketamine-like effects after recreational use of methoxetamine. *Ann Emerg Med*. Jan 12: 60(1):97-99.

Javitt DC (2007) Glutamate and schizophrenia: phencyclidine, N-methyl- D-aspartate receptors, and dopamine-glutamate interactions. *Int Rev Neurobiol*, 78:69-106.

Kalir A, Teomy S, Amir A, Fuchs P, Lee, SA, Holsztynska EJ, Rocki W and Domino E (1984) N -allyl analogues of phencyclidine: chemical synthesis and pharmacological properties. *J Med Chem*, 27: 1267-1271.

Kalsi SS, Wood DM, Dargan PI. (2011) The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. *Emerg Health Threats J*, 4:7107. 7107 - DOI: 10.3402/ehth.v4i0.7107.

Morgan CJA and Curran HV (2011) Ketamine use: a review, *Addiction*, 107:27-38.

Shields JE, Dargan PI, Wood DM, Puchnarewicz M, Davies S and Waring WS (2012) Methoxetamine associated reversible cerebellar toxicity: three cases with analytical confirmation. *Clin Toxicol*, 50: 438-440.

Ward J, Rhyee S, Plansky J, et al. (2011) Methoxetamine: a novel ketamine analog and growing health-care concern. *Clin Toxicol (Phila)*. 49: 874–875.

Wood DM, Yew DT, Lam WP, Dargan PI. (2012) Chronic methoxetamine exposure in a mouse model demonstrates that methoxetamine is not a “bladder friendly” alternative to ketamine. *Clin Toxicol (Phila)*, 50: 694.

Wood DM , Davies S, Puchnarewicz M, Johnston A, Dargan PI (2012) Acute toxicity associated with the recreational use of the ketamine derivative methoxetamine *European Journal of Clinical Pharmacology*, 68(5), 853-856.

Zarantonello P, Bettini E, PaioA, Simoncelli C, Terreni S and Cardullo F (2011) Novel analogues of ketamine and phencyclidine as NMDA receptor antagonists. *Bioorganic Med Chem Letters*, 21: 2059-2063.