ACMD

Advisory Council on the Misuse of Drugs

Consideration of the Novel Psychoactive Substances ('Legal Highs')

October 2011

ACMD

Advisory Council on the Misuse of Drugs

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

25th October 2011

Rt Hon. Theresa May, MP
2 Marsham Street
London
SW1P 4DF

Dear Home Secretary,

The Advisory Council on the Misuse of Drugs (ACMD) committed to providing the Government with advice on novel psychoactive substances (often colloquially termed 'legal highs'). This is a relatively recent phenomenon, exemplified by the drug known as mephedrone. The actions by the ACMD and subsequently by the Government on this drug have gone some way to reducing the potential harms caused by this substance. However, there is more that can be done.

The advent of novel psychoactive substances has changed the face of the drug scene remarkably and with rapidity. The range of substances now available, their lack of consistency and the potential harms users are exposed to are now complex and multi-faceted. In light of this we have pleasure in enclosing the Council's report.

This report provides advice on high level issues that ACMD believe the Government should give careful consideration to in addressing legally available psychoactive substances. The report does not purport to provide a single solution to the problem, but rather a number of practicable options that, in combination, seek to tackle the on-going sale, supply and consequential harms.

It is important that the Government recognises that each and every department, that has a locus of responsibility in drug issues should both take personal ownership and share collective responsibility of the recommendations in this report. Tackling the issues that are raised by novel psychoactive substances requires a co-ordination of efforts that can only be realised by a strategic and co-operative approach. The ACMD has

identified lead departments for each of the recommendations that should assist and guide the Government in this aim.

The ACMD provides key recommendations in this report on legislation, public health, education and research. The key legislative measures are primarily concerned with tightening the enforcement of existing legislation and moving the responsibility for the supply of novel psychoactive substances to the vendors, such that the burden of proof falls to them. The ACMD believe it is for vendors to prove that such substances are neither analogues of current medicines nor products harmful to consumers in their intended form. The ACMD also makes key recommendations around public awareness from local to international initiatives.

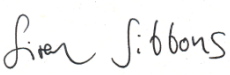
The production of this report has been greatly aided by valuable contributions from a wide range of organisations and experts. The Council is particularly grateful to those experts who provided written and oral evidence.

We will welcome an opportunity to discuss the report with you in due course

Yours sincerely

Professor Les Iversen
Chair, ACMD

Professor Simon Gibbons
Chair, Novel Psychoactive Substances Working Group



Cc:
Lord Henley
Anne Milton

Contents

Executive Summary

1.1 The Advisory Council on the Misuse of Drugs (ACMD) was requested to consider the issue of Novel Psychoactive Substances (hereafter, termed 'NPS') as one deserving careful and priority consideration. This issue has been a priority for the ACMD and of this Government[1].

1.2 This report provides high level advice to the Government on various practicable policy and legislative options that would tackle the on-going sale, supply and consequential harms associated with NPS and considers areas for research.

1.3 The issue of NPS[2] (often termed 'legal highs') is not recent, but has become prominent due to a range of complex factors, including: chemical technologies, market availability, internet supply, trends in substance misuse, price and others.

1.4 Generally legally available, NPS fall, broadly, into four categories:

i) Products with names which give no indication of what they contain;

ii) Named and specific substances which are designed to be similar chemically and/or pharmacologically to known specific controlled drugs;

iii) Substances related to medicines; and,

iv) Herbal and fungal materials or their extracts.

The issue

1.5 While a number of NPS have been controlled under the Misuse of Drugs Act 1971, e.g. piperazines including benzylpiperazine (BZP), synthetic cannabinoid receptor agonists and cathinones including mephedrone, among others, a number of synthetic chemicals designed to mimic the action of compounds such as amphetamines and ecstasy, or other controlled substances continue to be legally available.

1.6 The marketing and sale of NPS is often designed specifically to avoid legislation under the Medicines Act 1968 and NPS are therefore often marketed as '*not for human consumption'* and may variously be described as '*plant food'* or other terms. No safety data are provided with the materials and labelling is commonly as '*research chemicals'*.

[1] http://www.homeoffice.gov.uk/publications/alcohol-drugs/drugs/acmd1/ACMD-letter-home-sec-priorities?view=Binary

[2] See section 2 for a definition.

1.7 In the UK NPS are traded openly on the internet and in 'head shops'. This remains a very difficult trade to control. NPS may more often than not be purchased from overseas websites.

1.8 A large number of NPS are currently available in the UK from several different chemical classes with no data in relation to their pharmacology, chemistry, toxicology or safety assessments. The potential risk in the human use of such untested substances is obvious.

1.9 Reliable data on the prevalence of use or societal impact of NPS are difficult to obtain. Surveys of young people suggest that 20 to 40% have ever tried NPS and in the case of mephedrone (pre-ban) one survey indicated 34% had used in the past month, although these may be heavily biased samples (see British Crime Survey data table 1 & mixmag survey table 2).

1.10 The harms of NPS are multi-faceted and may be physical (intrinsic to the drug) or social in nature. Health services are starting to see health and other problems caused by regular use of NPS affecting NPS users' employment and education. Cases of dependence which require detoxification and psycho-social treatment (e.g. GHB (gamma-hydroxybutyrate)/GBL (gamma-butyrolactone)[3] dependence) are also presenting to specialist substance misuse and other services (sexual health services, youth support services etc) (ACMD, 2008).

1.11 There is an upward trend in admissions, due to NPS drug toxicity, for both hospital and pre hospital presentations. Most presentations show similar characteristics to stimulants such as cocaine, MDMA and amphetamine (*pers comm*, Dr David Wood, Dr Paul Dargan). The ACMD believes that particularly when new substances emerge that users have no experience of using, this may result in greatest harm before knowledge and understanding of a particular drug and its effects.

1.12 Further the ACMD understands that most people using NPS are not coming to the attention of specialist drug treatment services or general health services. Further, most people currently obtain information about NPS from their peers or from internet sites where drug using experiences are shared. The ACMD remains particularly concerned about under 16s using NPS.

1.13 Data from the National Programme on Substance Abuse Deaths (np-SAD) shows that there are 42 confirmed mortalities associated with one of the first NPS, mephedrone (see annex C).

[3] Gamma hydroxybutyrate and 1-gamma butyrolactone

1.14 Many of the NPS's are synthetic amphetamine-like pyschostimulants and are likely to share many of the well - documented adverse effects and dependence liability of the amphetamines. It can be predicted that the most potent substances are most likely to give rise to a risk of overdose, since the human dose is measured in a few milligrams, an amount equivalent to a grain of sugar.

Recommendations are listed in brief below for more details see chapter 12.

1.15 The UK should be pro-active in developing EU and international networks to address the issue of NPS.

1.16 Further, steps should be taken at EU level to encourage source countries to halt the manufacture of such substances.

1.17 For the Government to consider how to expedite the process of updating the Misuse of Drugs Act 1971 where more minor amendments to generic definitions are required e.g. cathinones, synthetic cannabinoids, tryptamines, phenethylamines and ketamine derivatives.

1.18 The application of the Act would be aided by continued capability developments in the area of chemical standards, analytical capability and forensic detection of compounds.

1.19 Explore the possibility of new legislation similar to the Analogue Act (1986) used in the USA and similar laws in other countries, in conjunction with generic definitions of chemical scope.

1.20 The powers available to the MHRA in the European Pharmaceutical Directive (Medicines Act 1968) should be fully utilised to prosecute the sale of NPS. The burden of proof should be placed upon the supplier to establish beyond reasonable doubt that the product being sold is not for human consumption and is safe for its intended use.

1.21 The powers available in the Consumer Protection from Unfair Trading Regulations (2008) (CPRs) and General Product Safety Regulations (2005) (GPSRs) should be fully utilised to control the trade in NPS. If the Regulations are considered lacking in this respect, then thought should be given to amendments so that the legislation can be brought to bear.

1.22 Provide resources for research on novel psychoactive substances and encourage all research councils to put out calls in these areas.

1.23 Request the Advertising Standards Authority (ASA) to investigate claims made by NPS websites.

1.24 Continue to strengthen public awareness and education of the dangers of using substances for which no safety data exists, using the most up-to-date IT methods (FRANK). The ACMD recommends that the government raise public awareness around NPS and implements strategies to reduce the demand for NPS by including NPS in substance misuse education in schools; developing targeted prevention initiatives and also treatment for those with acute problems (e.g. within A&E) and dependency.

2. Background

2.1. The ACMD was established under the Misuse of Drugs Act 1971 (hereafter termed the 'Act') and its purpose is to keep under review the drugs situation in the UK and provide advice to ministers. That advice may be concerned with; restricting availability, facilities and treatment (recovery), promoting co-operation between professional and community services, educating the public and promoting research.

2.2. This report is concerned with advice on the issue of Novel Psychoactive Substances (hereafter shortened to NPS), sometimes known as 'legal highs'. NPS are drugs which mimic, or are claimed to mimic, the effects of illegal drugs. There is a common, but mistaken, perception that because such drugs are not legally controlled or banned they are safe. None of them, however, have been subjected to anything approaching the stringent testing procedures which are required before a new medicine for human use is granted a license and, consequently, there is a significant risk of short- and long-term adverse effects resulting from their use

2.3. The Home Secretary indicated in correspondence with the ACMD, of February 2011, the importance attributed to the issue of Novel Psychoactive Substances. The ACMD similarly shares the concerns of the Government and considers the issue of newly emerging NPS as one which should be afforded careful and priority consideration.

2.4. The media has publicly charted the rise in prevalence of NPS. The issue was first brought to the fore in the media with the marketing of 'Spice' (an herbal material adulterated with a synthetic cannabinoid) products (Annex B) and subsequent intense interest in mephedrone and other compounds.

2.5. The ACMD has previously advised ministers on a number of NPS, e.g. BZP, spice and the cathinones (see ACMD reports and Annex B).

3. Introduction and scope

3.1. The ACMD define NPS as:

> *'psychoactive drugs which are not prohibited by the United Nations Single Convention on Narcotic Drugs or by the Misuse of Drugs Act 1971, and which people in the UK are seeking for intoxicant use'*.

3.2. Generally legally available, NPS fall, broadly, into four categories:

> i) Products with names which give no indication of what they contain;
>
> ii) Named and specific substances which are designed to be similar chemically and/or pharmacologically to known specific controlled, drugs;
>
> iii) Substances related to medicines; and,
>
> iv) Herbal or fungal materials or their extracts.

3.3. The Government has widely disseminated the statement that:

> '*just because a substance is termed 'legal' this does not make it safe, nor may it be legal'.*
>
> The premises in this statement are true and will be explored in this report.

3.4. This report's purpose is to provide consideration and advice on ways in which the Government can reduce the overall harms of NPS, develop options for reducing the demand for, and availability of novel psychoactive substances and to provide a more detailed consideration of the issue for the future.

3.5. This report is not intended to provide any specific recommendations on those NPS that should or could be controlled, (it should not be inferred that the NPS mentioned in this report should consequently be controlled).

3.6. The report will cover those NPS which are currently used and consider:

> i) The social and physical harms attributed to the use of NPS;
>
> ii) Both UK domestic legislative vehicles e.g. Misuse of Drugs Act 1971; Temporary Banning Powers; the Medicines Act 1968 and Trade Descriptions Act 1968 and the feasibility of developing other legislation including 'analogue legislation' – such as that used in the US;

iii) Outlining challenges in relation to forensic analyses of NPS; and,

iv) Measures to restrict the supply and demand of NPS. The report will outline some educational and other measures to this objective.

3.7. The report considers where there are gaps in the evidence base and in capability where there should be investment and research.

3.8. The importance of this report and its potential value can be highlighted with the examples of two case studies:

3.8.1. *Mephedrone*
The increase in the use of mephedrone in 2009/10 and its widespread marketing across Europe was alarming, particularly for the rapidity with which the drug became first choice for users. Its detection and identification prompted its consideration by the ACMD, who undertook an evaluation of the harms of the drug and concluded that it possessed similarities to existing pyschostimulants. Consequently, the ACMD advised the Government that it should be controlled, under the Act, as a Class B substance (for details see Annex B).

3.8.2. *2-DPMP (desoxypipradrol)*
Early analysis indicated that the drug 2-DPMP was being marketed as 'Ivory Wave' in 2010. The ACMD was sufficiently concerned by early reports of A&E admissions for this substance to recommend it to be subject to controls under the Open General Import Licence in October 2010. The ACMD have reviewed the profile of 2-DPMP (ACMD, 2011) and recommended that 2-DPMP and related analogues be controlled as Class B substances under the Misuse of Drugs Act 1971 (this advice was subsequently accepted by the Government). Meanwhile other psychoactive substances have been detected in test samples of 'Ivory Wave'. Earlier test samples of 'Ivory Wave' contained the banned cathinone, MPDV (methylenedioxypyrovalerone), and more recent analyses have detected diphenylprolinol, another pipradrol analogue (which are included in the generic definition described above).

4. The changing drug scene

4.1. It is important to note that overall drug use is coming down in the UK (British Crime Survey 2010/11). However, a significant recent development has been the increasing appeal of a range of new and easily available NPS.

4.2. The marketing and sale of NPS is often designed specifically to avoid legislation under the Medicines Act 1968. NPS are often marketed as '*not for human consumption'* and may variously be described as '*plant food'*, '*fish food'*, '*room odoriser'* or other terms. No safety data are provided with the materials and labelling is commonly as '*research chemicals'*.

4.3. Some materials are sold as 'legal high' products with a trade name but no indication of the active ingredients, while others are sold as 'research chemicals' under a specified chemical name. Both are often of un-reliable quality. Analysis of products has shown that the contents of branded products can change markedly from batch to batch, while the 'research chemicals' often turn out to be other than the chemical declared (see paragraph 5.2 below).

4.4. The chemists responsible for developing these new products have a sophisticated knowledge of the chemical/pharmacological scientific literature and the law. The example of mephedrone followed within a few months by naphyrone demonstrates how quickly this new industry can adapt to changes in the law to find markets to exploit.

4.5. Evidence suggests that the majority of NPS are currently imported from China - primarily in air freight and the post. There is a significant challenge for border agencies in identifying the true nature of the substances that are presented as 'white powders' and declared at importation as a variety of chemicals - many of which are wrongly described. Some of the materials are banned, some subject to licensing, some are known as psychoactive substances (and legal), and some are not known and may or may not be novel psychoactive substances of misuse in the future.

4.6. Selecting consignments for examination at the border is presently conducted on a risk based approach - it is impossible to examine or scan all freight and parcels. Once a consignment is selected; specially trained officers, expensive health and safety equipment and new technologies are often needed to conduct the examination. Where the substances are found and cannot be identified, samples can be sent to forensic scientists for analysis and identification.

4.7. Once in the UK, legal psychoactive substances are traded openly on the internet and also via dealers on the streets and in clubs and pubs. Purchases of NPS may also be made from non-UK internet sites and then supplied from overseas (both EU and non EU). As

the sale and distribution is in ‘legal’ products it is a very difficult trade to influence or control.

4.8. The growth in the NPS market has brought a different type of ‘drug dealer’ with entrepreneurs seeing the business opportunity whilst the substance remains ‘legal’. This has meant that once a substance has entered the drug scene the market can be very quickly saturated with the new drug. Many people importing these new substances appear to have had no previous involvement in the illicit drug trade and are just in it to make a ‘quick buck’. They have included students who have set up websites to supply nationally and who also supply the local student population.

5. Harms

5.1. The harms of the use of NPS are multi-faceted and may be physical (intrinsic to the drug) or social in nature. The ACMD has considered the harms of previous, groups of NPS in its reports on 'Spice' (the synthetic cannabinoid receptor agonists) (ACMD, 2009a), mephedrone (ACMD, 2009b), the naphthylpyrovalerone analogues, including naphyrone (ACMD, 2010a) and 2-DPMP – desoxypipradrol (ACMD, 2010b).

5.2. Test purchasing of NPS and forensic studies have shown that the contents of products are variable (Davies *et al.*, 2010; Ramsey *et al.*, 2010; Brandt, *et al*., 2010 a,b,c; SOCA, 2011). Despite claims, NPS marketed as one substance often contain something different and the content of a product may vary from month to month. Furthermore, some substances described and sold as 'legal highs' in fact contain controlled substances - in particular cathinones such as mephedrone, butylone or fluoromethcathinone and piperazines such as benzylpiperazine, fluorophenylpiperazine or chlorophenylpiperazine. A recent report of forensic analysis of seized samples of NPS indicated that 19% of samples tested contained a controlled substance (SOCA, 2011).

5.3. There are two consequences of this.

1. The variation in content of these products, with the presence of psychoactive substances of variable potency and adverse effects puts users at risk of increased acute harm and toxicity associated with their use; and,
2. Users, particularly young people, who are in possession of what they think are 'legal highs' may well be in possession of controlled substances and could face the prospect of being subject to prosecution and a potential criminal record if found in possession of them by the Police.

5.4. More recent studies have shown that NPS may contain only caffeine. Caffeine at the doses found in these studies (1g per packet) can result in significant toxicity, particularly if the user takes the product thinking that it contains an NPS rather than caffeine (Davies 2011).

5.5. Most legally available novel psychoactive substances are sold with no data regarding their chemistry, pharmacology or toxicology, no safety assessments and no administration instructions. The risks inherent in using such substances that have not been subjected to any safety assessments are obvious.

5.6. Use of NPS (both alone and with other substances) can result in acute toxicity and serious harm. The use of NPS can also result in young people and adults putting themselves in situations where they

may be vulnerable or at risk of other harms (e.g. through collapse, intoxication, etc) including accidents and being victims of crime (e.g. sexual or physical assault).

5.7. Many of the NPS's are synthetic amphetamine-like pyschostimulants and are likely to share many of the well documented adverse effects and dependence liability of the amphetamines. It can be predicted that users of the most potent substances are most likely to be at risk of overdose and associated acute toxicity since the human dose is measured in a few milligrams (i.e. the equivalent of a few grains of sugar).

5.8. The paucity of information on the pharmacology and toxicology of most NPS makes it hard to understand their possible dangers, or even to know what substances are contained in products branded as 'Ivory Wave' or 'Meow Meow'. For example, forensic analysis has revealed that the psychoactive substance present in 'Ivory Wave' has varied between samples. Analysis of test purchase samples and biological samples from individuals presenting to hospital with acute toxicity associated with NPS demonstrate that this is a rapidly changing market; analysis shows that numerous new legal drugs are being taken within a number of different classes and groups of drugs.

5.9. Acute recreational drug toxicity is a common reason for presentation to both hospital and pre-hospital medical services. It appears that, generally, the pattern of toxicity associated with NPS is broadly similar to that seen with classical stimulant recreational drugs such as cocaine, MDMA and amphetamine.

5.10. Obtaining information from hospitals on the patterns of acute toxicity associated with NPS can be difficult for a number of reasons:

i) Emergency Department and hospital staff are often not aware of these agents when they first become available and so they may be misrepresented in the medical notes. This was widely seen when patients first presented to hospital with self-reported mephedrone toxicity; some healthcare professionals were unaware of mephedrone and therefore recorded this in the notes as the synthetic opiate methadone. Although mephedrone and methadone have similar sounding names, they have very different pharmacological and toxicological actions.

ii) Healthcare professionals may contact the National Poisons Information Service (NPIS) for support in managing patients with acute recreational drug toxicity. The information collated by NPIS on acute NPS toxicity is reliant on the accuracy of the information provided to them by the treating physician. In addition, there may be a delay in on-line TOXBASE entries

being created on NPS as this requires the NPIS to be aware of the new drugs, and their associated harms to be able to draft a new TOXBASE entry.

iii) Hospital admissions are coded using an International system overseen by the World Health Organisation which is known as ICD-10. A number of studies have shown that this system is poor for coding acute recreational drug toxicity as a whole and even poorer for NPS as these drugs are not included in the coding system (Wood *et al*., 2011a; Shah *et al*., 2011). Furthermore, UK hospital admission data collated through the Hospital Episode Statistics (HES) based on the ICD-10 coding system currently only captures those patients that are admitted to hospital and does not include data on those discharged directly from the Emergency Department. The experience of Guy's and St Thomas' NHS Foundation Trust Clinical Toxicology Service is that up to 50% of patients with acute recreational drug toxicity are discharged directly from the Emergency Department. Therefore, for a number of different reasons, the HES dataset significantly under-estimates the true burden of acute toxicity associated with the use of NPS.

iv) Toxicological screening of blood and/or urine samples in patients presenting to hospital with acute recreational drug toxicity is not routinely undertaken as these patients are managed on a clinical basis and the results of comprehensive toxicological screening will not be available in a time-frame to be able to influence management decisions. Screening is generally only undertaken in specialist clinical toxicology centres for research purposes.

v) Finally, when toxicological screening is undertaken the ability to detect NPS depends on the expertise of the laboratory undertaking the analysis and the comprehensiveness of their analytical libraries of reference compounds.

5.11. The initial information on the patterns of acute toxicity and adverse effects associated with the use of NPS often comes from unsubstantiated internet based user discussion forums. Subsequent reports typically come from specialist hospitals with clinical toxicology services with an interest in acute recreational drug toxicity and specifically in NPS acute toxicity. Initially, these are often single case reports or case series which may attribute toxicity to the 'legal high' based on self-reported use rather than analytical confirmation; these reports come both Emergency Departments, clinical toxicology services and poisons information services (Wood *et al*., 2011b; Regan *et al*., 2010; James *et al*., 2010; Centres for Disease Control and Prevention, 2011; Personne and Hulton, 2008).

Publication of case reports / small case series is becoming more difficult and there is the potential that this may become a less available source of information on this topic. Analytical confirmation of the NPS responsible for toxicity is essential because a number of studies have shown that the content of various products purchased both from the Internet and street level drug dealers is variable and unreliable (Davies *et al*., 2010; Ramsey *et al*., 2010; Brandt *et al*., 2010a,b). Therefore, attributing toxicity to a particular substance based on self-reported use may result in an inaccurate representation of the toxicity associated with individual chemicals.

5.12. Despite these barriers, specialist clinical toxicology services working together with analytical toxicology laboratories with the necessary equipment and expertise to be able to screen for novel psychoactive substances can provide detailed data on the patterns of toxicity associated with NPS. In the last 4 years the clinical toxicology service, at Guy's and St Thomas' NHS Foundation Trust in South East London, has detected 14 NPS in patients presenting to hospital with acute 'recreational' drug toxicity (Wood *et al*., 2007; Dargan *et al*., 2008; Lidder *et al*., 2008; Wood *et al*., 2008a, Ovaska *et al*., 2008, Wood *et al*., *2008b*; Wood *et al*., 2009; Wood *et al*., 2010 a,b; Wood *et al*., 2011c). These include drugs from a number of different classes including the cathinones (e.g. mephedrone; methylone; methylenedioxypyrovalerone (MDPV) and butylone); piperazines (e.g.1-benzylpiperazine, trifluoromethyl-phenyl-piperazine); the pipradrols (D2PM diphenyl-2-pyrrolidinemethanol); and benzodifurans (e.g. Bromo-DragonFLY). A number of other groups have also reported cases or small case series of acute toxicity associated with analytically confirmed NPS (Derungs *et al.*, 2011; Sammler *et al*., 2010; Thorlacius *et al*., 2008, Gee *et al.*, 2008; Gee *et al*., 2010/a,b). Overall, the pattern of toxicity seen with NPS is significant and similar to that previously described in association with classical stimulant recreational drugs such as cocaine, MDMA and amphetamine. The clinical features seen in patients with acute toxicity associated with NPS include agitation, psychosis, delirium, tachycardia, hypertension, chest pain and seizures.

5.13. Some health services have started to see acute health and other problems caused by the chronic use of NPS. In addition to immediate acute health effects, they can have secondary effects and impact on NPS users' employment and education. For the formerly available NPS gamma-hydroxybutyrate (GHB) and gamma-butyrolactone (GBL) there have been reports of cases of dependence which require detoxification and psycho-social treatment.

5.14. These levels of problematic use require health professionals to develop treatment interventions to enable NPS users to try and stop use of these substances becoming regular or problematic, and

treatment for those with dependence or ongoing health problems caused by NPS.

5.15. Data from the National Programme on Substance Abuse Deaths (np-SAD) shows that 42 mortalities have been confirmed as associated with one of the first NPS, mephedrone (see annex C).

6. Use and societal impact

6.1. The availability and use of NPS is such a recent phenomenon that reliable data on prevalence of use and societal impact is difficult to obtain and, in many cases, is not available.

6.2. In July 2011, the British Crime Survey (BCS) reported its annual household survey findings for 2010 when mephedrone and other cathinones were added for the first time (British Crime Survey, 2011). This has provided the first national prevalence figures on these compounds. Table 1 shows that in 2010, the use of mephedrone (1.4%) was at a similar level to ecstasy use (1.4%) among those aged 16 to 59 (the third most used drug within this age group). For those aged 16 to 24, mephedrone use (4.4%) was at a similar level of use as powder cocaine (4.4%; the second most used drug amongst young people.

Table 1: Proportion of 16 to 59 year olds by age band reporting last year use of recently classified drugs, 2010/11 (BCS, 2011).

Percentage		England and Wales, BCS Adults aged 16 - 59	
Substance	**All**	Adults aged 16 to 24	Adults aged 25 to 59
Spice (and other cannabinoids)	**0.2**	0.4	0.1
BZP	**0.1**	0.2	0.0
GBL/GHB	**0.0**	0.1	0.0
Khat	**0.2**	0.3	0.1
Mephedrone	**1.4**	4.4	0.6
Unweighted base[4]	***27,450***	*3,667*	*23,783*

[4] Base numbers relate to Spice use. Bases for other drug measures will be similar

6.3. Dargan *et al* (2010) conducted a survey of mephedrone use in 1,006 individuals in schools, colleges and universities in an area of Scotland. The survey data were collected in February 2010, two months prior to the UK control of substituted cathinones in April 2010. Lifetime prevalence was 20%, ranging from 23% having tried it just once through to 4% reporting daily use.

6.4. Mixmag dance music magazine and associated website "DontStayIn" (surveygizmo.com) conducts annual online surveys with a sample of its readers. Data for the 2010 survey were collected in late 2009, several months before the controls on mephedrone were implemented. The 2011 Mixmag survey was conducted about six months after legislation was introduced, thereby allowing a comparison in mephedrone before and after

control. Two key limitations to the study are that firstly, it is a self selecting online sample and therefore unrepresentative of either the general population or the clubbing community and secondly, because it is a cross sectional rather than longitudinal survey the results are not directly comparable from year to year as the composition of the sample will slightly alter. However, the Mixmag brand has considerable loyalty amongst clubbers, evident in the number of respondents who trust enough to give their mobile phone number for follow up interview.

6.5. The findings on mephedrone use in 2010 and 2011, from the Mixmag survey (Mixmag, 2011), are summarised in tables 2 and 3 below, showing that recent (past month) mephedrone use fell by about one third after the ban was introduced. In terms of price and purity, users reported that the price of mephedrone had roughly doubled from about £10/g to about £20/g from late 2009-late 2010, with a shift from purchasing from websites to purchasing from dealers and most users now suspecting that the mephedrone they consume has been adulterated with other agents. The extent of the street market is not comparable to the previous internet trade, unsurprisingly, with the proportion of users reporting easy access to the drug halving between late 2009 and late 2010.

Table 2. Use of mephedrone. Self reported data from the Mixmag survey (Mixmag, 2011)

Use	2010 (pre-ban)	2011 (post ban)
Lifetime Use	42%	61%
Past year use	37%	51%
Past month use	34%	25%
Availability (easy or very easy to obtain mephedrone)	75%	38%

Table 3. Sources of supply of mephedrone, price and whether cut. Self reported data from the Mixmag survey (Mixmag, 2011)

Supply	2010 (pre ban)	2011 (post ban)
Websites	33%	1%
Dealers	24%	58%
Price	£12.20/g	£19.30/g
Suspect it was cut	30%	80%

6.6. An online survey of over 1,000 mephedrone users recruited from forums which attract experienced drug users (Carhart-Harris *et al*., 2011) reported that 30% stockpiled mephedrone in anticipation of ban; 64% said they used mephedrone less now it was illegal and 47% said mephedrone was noticeably less available after the ban.

6.7. In terms of displacement, 49% said that they would use more MDMA now that mephedrone was banned. The survey also

reported a range of concerns arising from mephedrone use with 13% of users saying they said or did things that they later regretted after taking the drug (Carhart-Harris *et al*., 2011); 14% feeling unable to stop taking mephedrone until they had used up all of their supplies; 11% reporting very strong cravings for mephedrone after having run out of stock and 14% describing it as very addictive.

6.8. Both the Mixmag survey (Mixmag, 2011) and the Carhart-Harris *et al* (2011) survey are limited by their design: they recruited self selecting samples of internet users who we might anticipate to be unrepresentative of the general population and disproportionately drug-experienced given the content of the websites on which the surveys were advertised.

6.9. A series of 3 surveys conducted in 'gay-friendly' dance clubs in South London with a convenience sample of club customers found that mephedrone had leapfrogged over cocaine and ecstasy to become the most popular drug on the fieldwork night despite having been controlled over two months prior to the surveys,(Measham *et al*, 2011a). Although overall levels of drug use are much higher amongst this sample of predominantly gay clubbers than in the British Crime Survey, the ranking of drugs – mephedrone, then cocaine, then ecstasy – reflects the findings of the British Crime Survey regarding self reported past year drug use amongst young adults, discussed above. Furthermore, there was evidence that an illegal street market had developed in mephedrone both inside and outside the South London dance clubs. However, there was little evidence of displacement to so-called second generation legal highs such as NRG-1, whose unknown content and misbranding were raised as concerns by Brandt *et al* (2010).

6.10. In the north west of England, surveys have been conducted with convenience samples of customers in the night time economies of four towns and cities in Lancashire in late 2010, more than six months after mephedrone and other substituted cathinones were banned (Measham *el at*., 2011a). Levels of self reported previous and current mephedrone use were much lower amongst these night time economy (predominantly bar) customers than amongst clubbers.

6.11. Also noted in these Lancashire night time economy surveys was the distinct local terminology for legal highs – white powders are known locally as 'Bubble' – with users unclear about the content or the legal status of this drug (Measham *et al* 2011b). The researchers noted that many users appeared to be uncertain of the content of 'Bubble' but moreover, seemed unconcerned by this.

6.12. The number of different classes of NPS makes predictions as to which will have the greatest impact and popularity uncertain, nevertheless NPS use appears firmly embedded in the UK drug

scene. It is highly likely that NPS with similar levels of popularity to mephedrone will appear in the future.

6.13. In applying the Misuse of Drugs Act 1971 to NPS it is important to understand that such action may have unintended harmful consequences – as described in the Demos/UK Drug Policy Commission report (2011). In addition to criminalising users, a criminal black market may emerge to supply the drug, with the temptation to introduce potentially harmful adulterants – as appears to have happened for mephedrone. These adulterants include caffeine, lidocaine, benzocaine and other substances commonly found in classical recreational drugs such as cocaine. The adulterants may have their own inherent toxicity that can be additive to the toxicity related to the NPS.

7. Measures to reduce supply

Use of the Misuse of Drugs Act 1971

7.1. The ACMD consider that the Act should be the primary legislation that Government uses to tackle supply side activity. However, the Act, and indeed other forms of legislation, can only be brought to bear if there is adequate capability and opportunity for detection.

7.2. Many new drugs are variations around central chemical backbones. The ACMD previously recommended generic controls to cover any closely related, harmful analogues. However, such generic definitions cannot cover all potential analogues, nor are they intended to. There have been recent examples (cathinones and synthetic cannabinoids) where analogues not covered by the original generic scope have been developed and marketed as NPS. In such cases, it would be advantageous to have a system whereby the Act could be updated, not by a separate definition, but as an update of the present or generic definition. At present, some families of drugs have layers of interrelated Statutory Instruments making the legislation difficult to navigate.

7.3. The detection of NPS is the single most limiting factor in the use of the Act to bring its penalties to bear on the issue. The two elements that comprise detection are firstly capability to analyse for a given substance and secondly detection of the drug at the point of import and through the supply chain to possession. Sophisticated methods of chemical analysis are needed to detect and identify these novel substances, for many of which no standard detection tests are available.

7.4. The ACMD recognise the work of the Home Office under the Forensic Early Warning System (FEWS) that seeks to address two major issues: firstly, identifying new compounds of use and developing reference standards and secondly, developing technologies for identification and enforcement purposes.

7.5. The ACMD are also aware of the Home Office's development of the Drug Early Warning System project (DEWS). This project aims to develop networks and links between evidence providers so that information on NPS can be shared and disseminated.

Open General Import licence - UK Border Agency and Novel Psychoactive Substances

7.6. The UK Border Agency (UKBA) is responsible for ensuring that the UK border is secure by maintaining border controls through working with other UK law enforcement agencies, particularly SOCA and other international partners, to intercept drugs before they reach the UK border. The UK Border Agency is responsible in enforcing the bans under the Open General Import Licence (OGIL).

7.7. Unless a Home Office Drug Licence is held, or a specific exemption within the Act exists, drugs controlled under the Act are prohibited from importation, thereby becoming an assigned matter for UKBA under the provisions of the Customs and Excise Management Act 1979, in respect of which enforcement activity can be undertaken. When a new psychoactive substance falls under the control of the Act, UKBA must treat that drug in exactly the same way as other controlled drugs. The drug can be seized only when imported improperly in contravention of a particular prohibition.

7.8. The control of compounds provides UKBA, and other enforcement agencies, the powers to intercept and, following confirmatory analysis, destroy the consignment at importation. Table 4 presents seizures by the UK Border Agency from 16 April 2010 to 31 August 2011.

7.9. In 2010 the ACMD recommended that desoxypipradrol be subject to restrictions placed upon it by importation under the Open General Importation Licence (Import of Goods (Control) Order 1954. This allows for an import ban but no penalties for possession.

Table 4. Seizures of recently banned substances by the UK Border Agency from 16 April 2010 to 31 August 2011.

Drug	Number of seizures	Weight (Kilos) (Litres)
Mephedrone (and related cathinones) **(16/4/10 –30/06/11)**	71	184kg
Naphyrone **(23/7/10-30/06/11)**	6	124.4kg
GBL, **(01/04/10 – 31/08/11)**	24	15.15 (L)

Police enforcement and the criminalisation of Young People

7.10. NPS present a particular challenge to the Police as many of the substances are white powders that resemble current controlled drugs. Added to this, the Police are also aware that many of the novel psychoactive substances contain controlled substances and without the assistance of accurate field testing devices, people in possession of substances are arrested on suspicion of possessing a controlled substance. The result will be either:

i) Detention in Police cells, interviewed then bailed pending forensic analysis and released from bail once analysis shows it to be a 'legal substance'

ii) As above but charged with possession when analysis shows the presence of a controlled drug.

7.11. As well as the potential waste of Police resources of investigating a substance which is not controlled, there is the very real problem of young people being criminalised through the possession of what they thought was a legal substance. Interactions between Police and young people have made it clear that the belief that these substances are 'legal and therefore safe' is the main driver for trying them.

7.12. As discussed in Chapter 4 the NPS market has introduced a new type of dealer and with it a new type of importer whom at this time, appear to be outside of the normal Organised Crime network. They are, nevertheless, making substantial profits and there have been Police operations against large-scale importers. However, such operations are hugely resource intensive, and have far from certain outcomes. There are many products sold by these importers and subsequently seized by Police, but the financial cost of submitting forensic samples to identify those that are controlled is very discouraging when considering future operations against NPS suppliers.

Medicines Act – Medicines Healthcare products Regulatory Agency (MHRA) and NSP

7.13. In addition to the Act, there are a number of measures that should be explored for the purposes of supply reduction. In the main this is focussed on other existing legislation outside of the Act such as Trading Standards, (consumer products regulations) and the Medicines legislation. The DEMOS / UK Drugs Policy Commission report (2011) also proposes use of consumer protection by existing legislation.

7.14. The Medicines Act 1968 is legislation within the portfolio of the Department of Health; this is now mainly based on the European Pharmaceutical Directive 2001/83/EC. The Directive is designed to ensure that only medicinal products with the appropriate

authorisation are advertised, sold and supplied in Member States. The licensing processes set out in the Directive mean that products meet relevant standards of safety, quality and efficacy (or traditional use for traditional herbal medicines).

7.15. If a product falls outside the definition of a medicinal product it is not covered by the medicines legislation. The responsibility for classifying products as medicines devolves to individual member states using the definition contained in Article 1 of the Pharmaceutical Directive 2001/83/EC. Guidance on how to interpret the definition has been given by the European Court of Justice in a number of Judgements over the years. In the UK the MHRA has issued guidance on this in Guidance Note 8 *A guide to what is a medicinal product* which is available from the MHRA website.

7.16. Article 1 of Directive 2001/83/EC defines a medicinal product as:

"Any substance or combination of substances presented as having properties for treating or preventing disease in human beings

Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis".

7.17. A product does not have to satisfy both parts of the definition to be a medicine, either is sufficient. A product has to be presented for human use in order to be considered under medicines legislation.

7.18. When considering substances of abuse or NPS the MHRA is not aware of any products being presented to treat or prevent disease. So far the MHRA has not issued any determinations under the first part of the definition in relation to products which might be regarded as substances of abuse or novel psychoactive substances.

7.19. When looking at products under the second limb, the MHRA has to demonstrate that the product has a significant effect on human physiological functions through a pharmacological, immunological or metabolic action. This approach has been set out clearly in a number of Judgements from the European Court:

"The pharmacological properties of a product are the factor on the basis of which the authorities of the Member States must ascertain, in the light of the potential capacities of the product, whether it may, for the purposes of the second subparagraph of Art 1(2) of Directive 2001/83/EC, be administered to human beings with a view to…restoring, correcting or modifying physiological function in human beings." HLH Warenvertriebs, 2005

7.20. Because of the European Court's approach the MHRA has had significant difficulties in classifying substances of abuse or novel psychoactive substances where data of suitable quality on the function and effect of the ingredients at the level contained in the product does not exist. The onus in cases of classification is on the MHRA to prove that a product has a significant effect, not for the person supplying the product to show that it doesn't. Because the Pharmaceutical Directive is not designed to regulate substances of abuse, products which are not presented for human use or which are presented for human use, but where there is no evidence of significant effect cannot be classified as medicines under the second part of the definition of a medicinal product.

7.21. Evidence for actions on human drug receptor or other targets *in vitro* may in future be obtained from collaboration currently being initiated with the US National Institute of Mental Health Psychoactive Drug Screening Programme, which will provide data from a wide range of such drug targets, and other biological research.

7.22. In the case of NPS, logic, reason and analysis to date says and demonstrates that many *are* being sold *and* used for the express purpose of their psychoactive effect (otherwise they wouldn't sell). It is somewhat perverse that the medicines legislation, set out to protect users from harmful products, has been presented to the ACMD as having little or no leverage in this area.

Consumer Protection Legislation (2008) and General Product Safety Regulations (2005) and Dangerous Substances and Preparations (Safety) Regulations (2006) – Business Innovation and Skills and NPS

7.23. The Consumer Protection from Unfair Trading Regulations 2008 (CPRs) prohibits the use by traders of unfair commercial practices in connection with the promotion, sale or supply of goods and services to or from consumers. The purpose of the CPRs is to protect the economic interests of consumers. The CPRs are subject to criminal and civil enforcement by the Office of Fair Trading and local authority trading standards officers.

7.24. Unfair commercial practices include:

i) Making false or deceptive statements; and;

ii) Omitting, hiding or providing unclear information which the average consumer needs in order to make an informed decision, where (in either case) this causes the average consumer to take a different decision.

7.25. Matters in respect of which false statements may breach the CPRs could therefore include statements that products would be effective as plant food or bath salts (if they would not) and statements that products originated in the EU (if they did not).

7.26. An example of an omission which could breach the CPRs could be a failure to state that a product could be damaging to human health. A clear statement that a product is not for human consumption would normally avoid the risk of such an omission. Such a statement might not be so effective if other statements by the trader, or the surrounding circumstances, created an *overriding impression* that the product was in fact intended to be ingested by the consumer notwithstanding the first statement. In that case the first statement might be seen as a sham and could breach the CPRs.

7.27. In each of these cases there is no breach of the CPRs unless the average consumer is misled by the false statement or the omission into taking a different decision. Where a commercial practice is directed to a particular group of consumers, reference to the average consumer is to be read as the average member of that group.

7.28. The purpose of the GPSR is to ensure that consumer products placed on the market, or offered or agreed to be placed on the market, or supplied or offered or exposed or possessed for supply, must be safe (the general safety requirement - regulation 5). The onus of ensuring safety is on the producer or distributor who is therefore liable if the GPSR are breached (see offences under regulation 20 of the GPSR).

7.29. In the context of psychoactive drugs sold as plant food or bath salts or other consumer product, there would be a breach of the GPSR if the producer or distributor placed the product on the market or supplied it intending it to be ingested and knowing this ingestion was dangerous to human health or safety. The ACMD considers that products are knowingly being supplied, in head shops and marketed on the internet, for human consumption. In addition, it is known that these products have a psychostimulant effect and can, in larger quantities, be harmful to health.

7.30. This is exemplified by those products sold as plant food which have clear instructions on them and provide a ‘dose for the plants’, or ‘warnings to gardeners’. Indeed, some websites even offer to sell analytical balances so that the user can measure a suitable dose of ‘plant food’; others offer advice on adverse consequences of accidental ingestion of ‘plant food’.

7.31. The ACMD does not believe such thin veneers of legitimacy should be an impediment to the legislative system and be accepted when the health of individuals is at risk.

7.32. Offences under the GPSR include the failure to provide appropriate information to consumers on inherent risks; failure to adopt measures which enable the receipt of information about risks posed

by products and to deal with such risks; and failure to monitor safety of products placed on the market. Thus if a distributor who was made aware or had reason to suspect that the plant food he was selling was in fact psychoactive drugs, that would be unsafe.

8. Measures to Reduce Demand

8.1. The UK Drug Strategy (2010) has two overarching aims which are:

- *"reduce illicit and other harmful drug use; and,*
- *increase the numbers recovering from their dependence*"

It recommends that demand for illegal drugs is reduced by:

"…*creating an environment where the vast majority of people who have never taken drugs continue to resist any pressures to do so, and making it easier for those that do to stop. This is key to reducing the huge societal costs, particularly the lost ambition and potential of young drug users*."

8.2. NPS present particular issues and challenges for demand reduction interventions. From analysis of trends in NPS use, it is apparent that those who use NPS are mainly young people or young adults (British Crime Survey 2011) who are experimenting or trying to enhance experiences (mainly at social events), or are those participating in clubbing and music events such as festivals (Mixmag Survey) NPS use is rarely 'dependent', though it can cause acute harm as discussed in previous chapter and often features mixing different drugs together and drinking alcohol.

Demand reduction

8.3. Demand reduction strategies for other types of substance misuse which could be applied to NPS include education, prevention, and treatment interventions. The evidence base that treatment can reduce and stop drug misuse is good. `Drug misuse and dependence: UK guidelines on clinical management' (2007) states "the effectiveness of well delivered evidence-based treatment for drug misuse is well established. UK and international literature consistently shows that drug treatment covering different types of drug problems…..impacts positively on levels of drug use". The evidence for education and prevention in reducing demand is weaker, though some interventions have been shown to increase knowledge and delay the onset of use thus reducing potential harmful use (Wenzel et al 2009).

9. Public health messages

9.1. It is vitally important that there is provision of accurate public health messages on NPS to allow potential users to understand the choices that they are making and the harms associated with NPS. Users may be unaware of the risks that they are taking with such substances. Existing mechanisms for delivering public health messages and drug education should include reference to NPS including public campaigns e.g. FRANK and public information campaigns.

9.2. There are health issues associated with NPS which particularly stem from the array of available compounds and, as aforementioned, the lack of consistency in product content and quality (see chapter 5). This array of compounds complicates the ability to provide clear messages on any given product – though presents opportunities to highlight the potential harm of taking unknown and potentially harmful substances.

Drug education and prevention

9.3. The ACMD supports the inclusion of NPS in universal drug education programmes in schools alongside other substances and over the counter medicines to increase knowledge and awareness of harms of NPS. The ACMD concurs with the previous DFEE guidance `Protecting Young People' (1998) which stated that research shows that;

- The impact of drug education on drug using behaviour has been shown to be limited. Drug education alone is unlikely to prevent young people from ever experimenting with drugs.

- 'Just Say No' and 'shock/ scare' approaches are likely to be ineffective and may even be counterproductive.
- Good quality drug education can impact on changes in specific drug using patterns and reduce the use of drugs and associated problems for young people.
- Drug education can contribute towards decreased harm and increased safety for young people, their families and communities.

9.4. The ACMD are also aware of the need to provide on-going and regular education and training on NPS to schools and youth services in order to keep abreast of changes in patterns in drug use – in order to be able to maximise drug education opportunities in schools and youth services. In addition there is also requirement to provide education on NPS to parents and families. The ACMD therefore consider that there are a number of areas where drug education and prevention strategies should be developed to align NPS with other substances.

9.5. The ACMD consider that innovative and bold use of new technologies which are used by young people and young adults including social networking sites, multimedia, smartphone applications and interactive websites may maximise opportunities to reach these populations. Educational `packages' using these methods and ICT technology may reach a range of groups who are thinking of using, or using NPS. If these media were used - it would be essential to ensure the information and advice provided is factual and evidence-based which outlines potential harms, challenges use and directs users to help but which does not preach or moralise.

9.6. **Targeted prevention**

9.7. The 2010 drug strategy places an emphasis on early intervention for those young people and families who are at increased risk of developing substance misuse problems, in particular Those who are truanting or excluded from school, looked after children, young offenders and those at risk of involvement in crime and anti-social behaviour, those with mental ill health, or those whose parents misuse drugs or alcohol - need targeted support to prevent drug or alcohol misuse or early intervention when problems first arise.

Evidence indicates that family focussed early interventions to strengthen functionality and parenting skills, and targeted support for young people in these circumstances will reduce the risks of the development of a range of problems including offending and substance misuse (Kendall, S., Rodger, J. and Palmer, H (2010).

Consideration of NPS information, education and interventions to prevent use in the context of this prevention work is recommended.

9.8. Targeted prevention interventions are also recommended for those who have begun to use – to deter use and prevent use being harmful or developing into dependence. This may include interventions specifically for certain groups of users such as clubbers and could include:

- tailored information (particularly on the risks of poly-drug and alcohol use and injecting `unknown substances'); website based information and advice;
- brief interventions to reduce or stop use (such as those provided for stimulant use and alcohol misuse);
- Localised on-site advice and help at festivals, clubs at other environments with a high likelihood of use - with staff trained in substance misuse
- referral pathways in each local area to young people and young adults and other substance misuse services.

These prevention initiatives will require `upskilling' of those in contact with new NPS users in NPS information, advice, emerging prevention, brief interventions and referral for treatment for those that need it. This may include la range of local young people and young adult services and young peoples substance misuse services.
`

Prevention and the drug using environment

9.9. As with other types of substance misuse the design and staffing of environments where supply or use is occurring can prevent use and reduce risk of harm associated with use (Brennan I., Moore S.C., Byrne E. et al). The application of this principle to NPS should be explored, particularly in relation to:

- club and festival site environments. Interventions could include: regular checks of toilet and `chill-out' facilities to minimise acute toxicity cases being left unattended; areas designed and lit to minimise use and maximise identification of individuals in need of help, toilets designed without flat surfaces that can be used to prepare drugs, staff trained in identifying use acting appropriately, staff trained in basic substance misuse identification, effects and resuscitation techniques etc.

- `Head shops': where legal substances are sold. Liaison is recommended with local drug and alcohol partnerships and shop owners and staff. These outlets may be an outlet for information, targeted prevention and even drug testing of supplies or samples.

Treatment

9.10. The treatment of acute toxicity is discussed in previous chapters. However, there is an emerging need to provide treatment for chronic NPS use and dependence. All local areas in England have young people's substance misuse services and a network of adult substance misuse services. The ACMD have heard evidence that services (including substance misuse services and sexual health services) are beginning to see NPS users. In addition to advice and information, these services can provide generic brief interventions and care planned support for substance misusers.

9.11. In response to emerging needs, several substance misuse services – specialising in treatment for NPS users with serious problems or dependence have been developed. Some of these services are seeing populations who do not identify themselves as requiring traditional 'drug treatment' and who state they would not attend conventional drug services. Most are self referrals, but some have been referred from club drug help lines or through liaison with local sexual health services, services for lesbian, gay, transgendered and bisexual people, GP's or accident and emergency departments.

9.12. Treatment protocols are being developed by these services including: specialist assessments; detoxification (in-patient and outpatient for substances including GHB/GBL); psychological and psychosocial treatment including cognitive behavioural therapy (CBT) and referral and support for drug-related health issues e.g. kidney and bladder problems for ketamine users. GHB/GBL withdrawal can result in severe and potentially life threatening symptoms. The club drug clinic in West London has been working with the Clinical Toxicology Service at Guy's and St Thomas' NHS Foundation Trust to develop in-patient and out-patient referral pathways and optimise the management of this group of patients

9.13. However, there is clearly a need to share current practice, evaluate new treatment interventions and research `what works' in treating NPS. This may require investment by commissioners and health research bodies to enable us to collectively build evidence-based practice and disseminate this.

9.14. There is also a need to specifically look for evidence of NPS use in local area needs assessment to inform the planning of local substance misuse education, prevention and treatment systems.

Building knowledge and evidence-based practice in demand reduction

9.15. A range of professionals will need to develop some basic competence in being able to provide NPS information and education, identify NPS-related problems and intervene or refer people for help. Core professionals requiring competence may include: young people and adults' substance misuse services, youth workers, sexual health services, and those delivering substance misuse education and prevention initiatives.

9.16. Building basic knowledge and competence in preventing harm from NPS is challenging due the pace of change of emerging NPS use. This may require implementation of initiatives to create an evidence-based knowledge base and share this knowledge with those responsible for training of core sets of professionals.

9.17. The ACMD recommend building on local and European initiatives that are emerging and show promise which the UK can learn from and collaborate with, for example ReDNet.

10. Current and future legislation

10.1. The primary vehicle for regulating harmful NPS is through the Misuse of Drugs Act 1971 (MDA). In controlling a substance under the Act there is a requirement for the ACMD to conduct a review of the evidence of harms. In addition, the ACMD will consider any application of a generic scope definition to cover harmful close analogues, although this may need updating as appropriate (see paragraph 7.2)

10.2. The coalition set out in its agreement that:

We will introduce a system of temporary bans on new 'legal highs' while health issues are considered by independent experts. We will not permanently ban a substance without receiving full advice from the Advisory Council on the Misuse of Drugs'.

10.3. The Government proposed a system of Temporary Class Drug Orders (TCDO) in 2010 as part of the Police Reform and Social Responsibility Bill. The Bill has received Royal Assent and is available at:http://www.legislation.gov.uk/ukpga/2011/13/pdfs/ukpga_20110013_en.pdf

10.4. The primary reason for having the new drug orders is one of responsiveness. The Government considered that the time taken to ordinarily control a given drug was not commensurate with the rapidity with which NPS have been seen to come onto the market and become part of users' repertoires.

10.5. The ACMD is supportive of these proposals. Overall the ACMD consider that the Drug Orders should be used sparingly and appropriately – they should not be a substitute for consideration of full control under the Misuse of Drugs Act 1971, but rather a proportionate mechanism with which to prevent harms of a drug where a swift response is essential.

10.6. The ACMD has been consulted during the development of the Bill, on the drugs clauses, and considers that it represents a positive legislative tool in reducing harms and also is committed to evidence-based policy making by maintaining, as with the Misuse of Drugs Act 1971, statutory consultation with the ACMD.

10.7. Critical to the successful implementation of a Drug Order will be the flow of evidence. In invoking an order, which will be done in a relatively short space of time, it will be important that the ACMD has access to that evidence which underpins the issue and that the evidence is appropriate and relevant to the consideration so that it may make an evidenced based and robust decision. Such evidence will include data from the Government's Forensic Early Warning

System (FEWS) and Drugs Early Warning System (DEWS). It is also critically important that resources be available to provide reference standards and to undertake risk analysis of NPS, including collecting data on the acute harm (toxicity) related to use of the NPS and where necessary, pharmacology studies to determine the activity of the NPS.

International Perspective

10.8. International bodies also consider whether substances should be controlled or not. For instance there are United Nations conventions covering narcotics and psychotropic drugs, and the World Health Organisation undertakes formal risk-assessments. The Council of Europe on 2 December 2010, following a formal risk assessment by the EMCDDA and Europol (EMCDDA & Europol, 2010), adopted a Decision submitting mephedrone to control measures (Council of Europe, 2010). Council of Europe. (2010). *Council Decision 2010/759/EU on submitting 4-methylmethcathinone (mephedrone) to control measures*. 2 December 2010. Strasbourg. Available at: http://www.emcdda.europa.eu/attachements.cfm/att_121058_EN_Council_Decision_2010_759_EU_2December_2010.pdf and EMCDDA. (2010). *Risk-assessment report of a new psychoactive substance: 4-methylmethcathinone (mephedrone)*. Lisbon: European Monitoring Centre on drugs and Drug Addiction. Available at:http://www.emcdda.europa.eu/attachements.cfm/att_116485_EN_Risk%20Assessment%20Report%20on%20mephedrone.pdf

10.9. However, the EMCDDA risk assessment reports, although detailed and thorough inevitably take considerable time to prepare – 12 months or more. The advice on mephedrone, for example, was limited to one substance and appeared some 9 months after the ACMD recommendation on this and other cathinones.

11. Analogue Legislation – legal and chemical aspects

11.1. Analogue legislation, in simple terms makes analogues of existing controlled substances automatically illegal. Analogues are defined as substances that bear a chemical and pharmacological similarity to existing controlled substances.

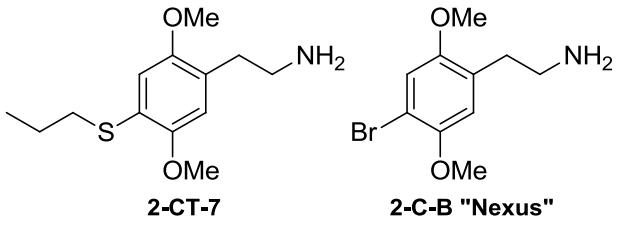
11.2. Many English speaking countries have 'analogue legislation' to keep up to date with the continually changing chemistry of new drugs.

11.3. The simplest and most litigated legislation is in force in the USA. Stripped of its legal language, the U.S. Federal Analogue Act 1986 outlaws a drug ('B') if it is substantially similar to the chemical structure of a controlled drug ('A') and either 'B' has a substantially similar psychoactive effect as 'A', or is intended to do so or is represented to do so.

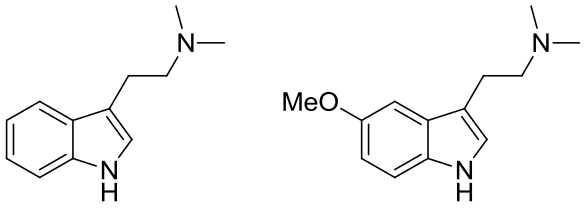
Advantages

11.4. Chemically, the US Analogue Act does have some advantages over the incremental generic approach to the classification of controlled substances. Many of the chemotypes of common drugs of abuse are well described and delineated, and in some cases it is very easy to see that novel psychoactive substances have close similar structure to an existing and controlled drug of abuse.

11.5. A recent presentation to the ACMD by the US Department of Justice and the Drug Enforcement Agency gave a number of examples where the Act was employed to control substances such as the simple phenethylamine 2-CT-7 which is structurally similar to 2-C-B.The similarity is due to replacement of the bromine atom on the aryl ring with a thio-propyl group (U.S. v. Niemoeller (Indiana 2003)).Other examples include simple tryptamine analogues. These compounds are psychoactive and are commonly found in nature in plants, fungi, microbes and amphibia and they are abused due to stimulant and hallucinogenic properties. Examples which are covered by the Federal Analogue Act include dimethyltryptamine (DMT) and its analogue 5-methoxytryptamine (5-MeO-DMT) and the clear structural similarity of these compounds; even to non-chemists is readily obvious (they are both available on Wikipedia).



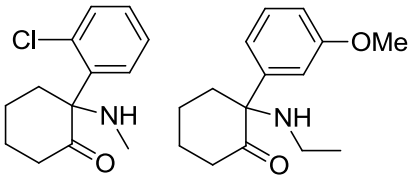
2-CT-7 **2-C-B "Nexus"**



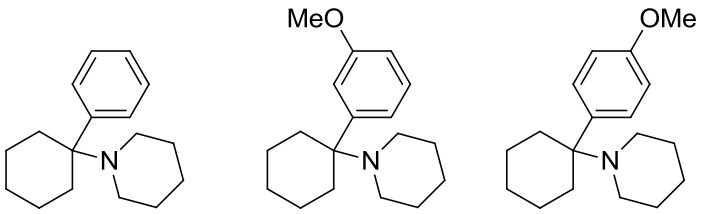
Dimethyltryptamine **5-MeO-dimethyltryptamine**

11.6. The same parallels can be drawn with reference to some of the newer NPS which are currently being sold through the internet. These include ketamine derivatives such as methoxetamine.

11.7. Ketamine is a Class C drug under the Misuse of Drugs Act 1971 and has use as an anaesthetic (Morgan and Curran 2011) whereas the legal high methoxetamine possesses a different substituent on the nitrogen atom and aryl ring to those of ketamine. At the present time, nothing is known on the pharmacology and toxicology of this compound. Methoxetamine is outside of the Misuse of Drugs Act 1971 but could arguably be controlled by an analogue legislation approach or by the Medicines Act 1968. Other striking and obvious examples where this approach could find utility include the new phencyclidine (PCP) NPS analogues which are appearing as NPS on the internet (3- and 4-



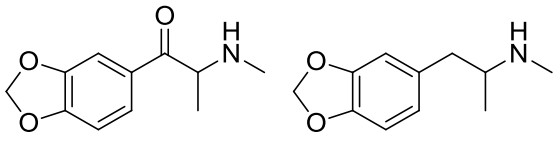
Ketamine **Methoxetamine**



PCP- phencyclidine **3-MeO-PCP** **4-MeO-PCP**

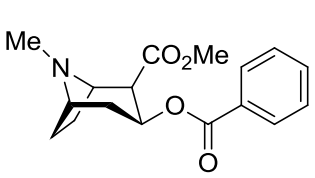
methoxy-PCP) which are highly structurally similar to PCP (“Angel Dust”), which like ketamine is also a dissociative anaesthetic and abused (McCarron et al., 1981). At the present time, little is known on the pharmacology or toxicology of this compound. However, there have been 3 recent analytically confirmed cases of acute methoxetamine toxicity in which the individuals presented with some features in keeping with Ketamine toxicity, but with more predominant stimulant effects than would be expected from Ketamine (Personal Communication: Dr Paul Dargan and Dr David Wood, Guy’s and St Thomas’ NHS Foundation Trust).

11.8. This highlights a general problem of the analogue approach. It is highly amenable to certain classes of drugs of abuse such as the phenylethylamines, including simple cathinones and amphetamines such as methylone and MDMA (“Ecstasy”), where similarity is readily apparent.

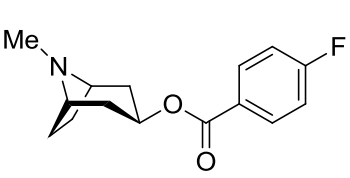


Methylone **MDMA ("Ecstasy")**

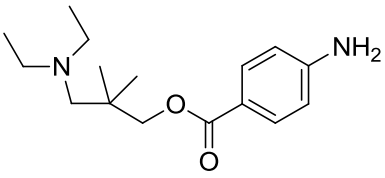
11.9. Similarly while it is easy to see that the novel psychoactive substances 4-fluorotropacocaine is structurally related to cocaine, the widely available 'legal high' dimethocaine (laroacine) appears to be very different.



Cocaine



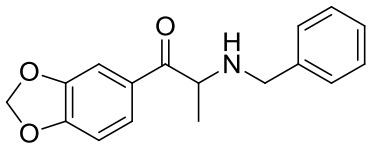
4-fluorotropacocaine



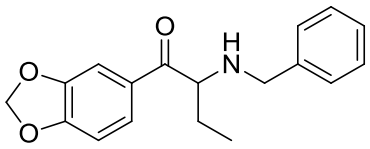
Dimethocaine

One chemist may argue that dimethocaine is highly similar as it contains an ester group and has a nitrogen atom that is substituted with alkyl groups just as is found in cocaine and that the distance of the nitrogen group to the ester group is also similar. However, another chemist may argue that dimethocaine is substantially dissimilar and the overall structural relationship between cocaine and dimethocaine *is not apparent or obvious*. Within the analogue Act, the onus is upon the Prosecution to demonstrate this similarity. If chemists can find disagreement upon structural similarity, then a jury is unlikely to be convinced in this specific case. Dimethocaine is indeed structurally related to cocaine, which was the basis for this class of anaesthetic (Wolverton *et al*., 1983).

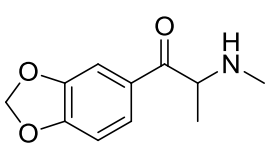
11.10. What is attractive about the analogue approach is that simple modifications can readily be covered. A good example of this is the recent formal report by Dr Les King to the EMCDDA of two cathinone derivatives, 2 benzylamino-1-(3,4-methylenedioxyphenyl)propan-1-one (BMDP) and 2 benzylamino-1-(3,4-methylenedioxyphenyl)butan-1-one (BMDB), both of which fall outside of the generic classification of cathinones but are clearly analogues of cathinones like methylone.



BMDP



BMDB



Methylone

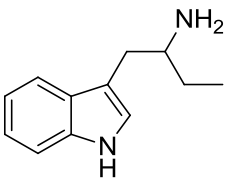
11.11. Perhaps a hybrid approach could be adopted where certain classes of compound would be covered by an Analogue Act and others by the more incremental generic approach.

11.12. From a chemical perspective, there are problems with the interpretation of "substantially similar structure" in the US definition of a chemical analogue, as it implies some qualitative measure of

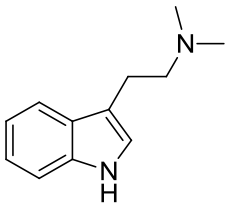
similarity (Shulgin, 1997). In chemistry, the term analogue is often used in a different context with a much wider meaning. Chemists also use terms like 'structurally related' for two compounds that share the same substructure (i.e. parts of the two structures share the same carbon skeleton), regardless of modifications to functional groups or heteroatoms (i.e. non-carbon atoms). Thus when comparing two structures, the qualitative aspect is much less important to chemists and therefore it is likely that there will be a wide range of interpretations of the term "substantially similar structure".

11.13 An example is a decision by a district court (USA v. Damon S. Forbes et al. (Colorado 1992)) where it was decided that α-ethyltryptamine (AET), which is not controlled in the UK, was not an analogue of *N,N*-dimethyltryptamine (DMT) or *N,N*-diethyltryptamine (DET). These compounds are all structurally related in that they all have a tryptamine substructure and most chemists would regard them as analogues in a chemistry context. The grounds for the decision were based on the fact that,

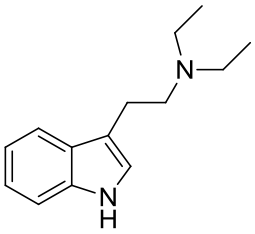
(i) AET was a primary amine whilst DMT and DET are tertiary amines,
(ii) AET cannot be synthesised from DMT or DET, and
(iii) the effects of AET are not substantially similar to those of DMT and DET.



Alpha-ethylltryptamine (AET)



Dimethyltryptamine (DMT)



Diethyltryptamine (DET)

11.14 Apart from the problems of the definition of chemical analogues, Analogue legislation, as exemplified by the US Federal Analogue Act (1986), has other potential drawbacks that have to be weighed against the potential benefits of this type of legislation. With analogue legislation the prosecution would rely on expert opinion from at least two expert witnesses, a chemist and a pharmacologist. Likewise the defence would call their own experts. This could lead to a "battle between experts" under the constraints of the adversarial system where open discussion is not possible. It could be argued that transferring the responsibility to a few individual experts is less equitable than the current system which uses the wide range of expertise in ACMD. The judicial process would be costly and take up valuable court resources.

11.15 The very purpose of analogue legislation necessitates some elasticity and prevents a specific definition of a chemical analogue. However, in the United States the scope of the legislation has become more restricted as interpretative case law has developed. Eventually the analogue legislation may be no better than a carefully considered generic definition. This is typified by the examples from US case law where 2-CT-7 was deemed to be an analogue of 2-C-B "Nexus" and 5-MeO-dimethyltryptamine was deemed to be an analogue of dimethyltryptamine. In both cases the modifications were foreseeable and were included within the scope of the generic definitions in the Misuse of Drugs Act 1971.

Suggested Approach

11.16 Despite these potential problems, on balance ACMD believes that there are positive features of analogue legislation and strongly recommends that serious consideration be given to an analogue approach to the regulation of NPS.

11.17 One approach to analogue definition would be to delegate the authority for the determination of what qualifies as a controlled substance analogue to a statutory body. In effect this is a part of what the ACMD already does when assessing new substances with reference to and by analogy to existing controlled substances and advising ministers on which substances merit control. In this sense ACMD have operated their own form of analogue legislation, e.g. GBL; synthetic cannabinoids; benzyl piperazine; cathinones; and desoxypipradrol. However, implementation of the ACMD recommendations is subject to the legal processes and cannot be fast tracked to deal with every new controlled drug analogue.

11.18 When a new NPS appears on the market, it is proposed that the statutory body would consider the available evidence and decide whether the drug is an analogue of a controlled drug and if so the drug would then become a controlled drug using a fast track system similar to the temporary class drug order but without the need for a full risk assessment after one year.

11.19 The proposed temporary class drug orders would then only need to be used for new 'legal highs' that are not considered by the statutory body to be analogues of controlled drugs.

11.20 It is notable that in Poland, which has one of the highest rates of NPS use in Europe, new legislation has been developed to allow analogues of controlled substances to be banned rapidly, using pharmacological similarity to controlled substance as an important criterion.(ReDNET News August 2011)

12 Conclusions and Recommendations

12.1 The following recommendations are high level issues that the ACMD consider should be addressed by relevant Government Departments at strategic levels and be embedded within long term policy. The ACMD understands that the issue of NPS (legal highs) is one that cuts across a number of Government Departments; therefore it is crucial that it is addressed by the Home Office with other Departments in equal measure. The ACMD believes that this issue requires a multi-faceted approach as new 'NPS continue to replace substances that are controlled.

Recommendation 1 and 2

12.2 The issue of NPS requires a cross boundary cohesiveness to ensure that markets are interrupted, supply side activities interdicted and new compounds identified early. Spreading the net of knowledge as wide as possible will be crucial in addressing this issue.

12.3 **Recommendation: The UK should be pro-active in developing EU and international networks to address the issue of NPS.**

12.4 **Recommendation: Further, steps should be taken at EU level to encourage source countries to halt the manufacture of such substances.**

Recommendation 3

12.5 This report demonstrates the fast pace of change in the field of NPS. Many new drugs are variations around central chemical backbones. The ACMD has previously recommended generic controls for drugs such as the synthetic cathinones. However, such generic definitions do not often cover all compounds, nor are they intended to.

12.6 Whilst it is the aim of the ACMD to ensure that those drugs that are harmful, with the potential for misuse, are covered by a generic definition, there will be those drugs that fall outside of it.

12.7 The ACMD fully recognise the importance of parliamentary process and its scrutiny in considering legislative changes for controlling new drugs. The ACMD are cognisant of the Lord's consideration of using the affirmative legislation procedure for strategy instruments laid for new drugs. This is a more stringent procedure than the negative resolution.

12.8 The ACMD are content with process whereby the ACMD provide recommendations to revisit and amend previous generic controls to previous NPS's.

12.9 However, where minor adjustments to the Act are required, to update it in-line with analogues of all closely related substances, the procedure as above is still required. An example of this was

naphyrone which was not covered by the original cathinone generic as it was deemed to be sufficiently chemically different, and would not have fitted well within the original cathinone generic (the ACMD produced a new report and a generic description on this substance three months after the original generic description).

12.10 In such cases, it would be expedient to have a process for updating the Act that was of minimal burden for Departmental and Parliamentary administration.

12.11 This issue is distinct from the process by which given drugs are classified e.g. the proposed Temporary Class Drug Order process or directly via the Misuse of Drugs Act.

12.12 **<u>Recommendation</u>: For the Government to consider how to expedite the process of updating the Misuse of Drugs Act 1971 where more minor amendments to generic definitions are required e.g. cathinones, synthetic cannabinoids, tryptamines, phenethylamines and ketamine derivatives.**

12.13 Lead Government Department: Home Office

Recommendation 4

12.14 Many 'NPS are mis-sold, being products that contain illegal compounds. The ACMD consider that the Misuse of Drugs Act should be brought to bear fully on those who are intent on supplying illegal drugs.

12.15 There is therefore a continual need to horizon scan and develop capability to ensure that enforcement agencies can fully discharge their duties under the Act.

<u>Recommendation:</u> The application of the Act would be aided by continued capability developments in the area of chemical standards, analytical capability and forensic detection of compounds.

12.16 Lead Department: Home Office

Recommendation 5

12.17 This report considered models of analogue legislation used in other countries to counter novel psychoactive substances that chemically and pharmacologically mimic controlled substances. The ACMD understands that similar legislation is in force in Australia and New Zealand. In particular the report focuses on the US Federal Analogue Act (1986) which is set out to address new substances that are similar in composition to controlled drugs. The ACMD believes this approach has its merits and can be used to counter the prevalence of novel psychoactive substances.

12.18 **<u>Recommendation</u>: Explore the possibility of new legislation similar to the Analogue Act (1986) used in the USA and similar laws in other countries, in conjunction with generic definitions of chemical scope.**

12.19 Lead Government Department: Home Office

Recommendation 6

12.20 Some NPS are analogues of licensed medicines, for example methoxetamine, an analogue of the anaesthetic drug ketamine, and methyl phenidate, an analogue of the Attention Deficit Hyperactivity Disorder (ADHD) medication (Ritalin).

12.21 The ACMD understands that the legislation administered by the MHRA (Medicines Act 1968) is now mainly based on the European Pharmaceutical Directive. The ACMD believes that more can be done by the MHRA to utilise the European Pharmaceutical Directive to prosecute the sale of unlicensed analogues of medicines which are NPS's, even where the labelling states 'not for human consumption' in cases where it is clear that the substance is in fact sold for human use.

12.22 Many NPS are sold as 'plant food'. It is clear that the vendors use the legislation as shelter when the intended purpose of the products is plainly clear. The ACMD does not believe such thin veneers of legitimacy should be an impediment to the legislative system and be accepted when the health of individuals is at risk.

12.23 **<u>Recommendation</u>: The powers available to the MHRA in the European Pharmaceutical Directive (Medicines Act 1968) should be fully utilised to prosecute the sale of NPS. The burden of proof should be placed upon the supplier to establish beyond reasonable doubt that the product being sold is not for human consumption and is safe for its intended use.**

12.24 Lead Government Department: Department of Health and the Medicines Healthcare Products Regulatory Agency (MHRA).

Recommendation 7

12.25 The ACMD believes that more can be done to counter the prevalence of NPS by utilising civil penalties, under the jurisdiction of the Department of Business, Innovation and Skills, e.g. consumer protection legislation, especially in those cases where misleading statements are made about any given NPS. Further the ACMD believes that there is a role here for the Trading Standards Institute to play, in relation to policing 'head shops' that sell NPS ('legal highs') with misleading statements.

12.26 **<u>Recommendation</u>: The powers available in the Consumer Protection from Unfair Trading Regulations (2008) (CPRs) and**

General Product Safety Regulations (2005) (GPSRs) should be fully utilised to control the trade in NPS. If the Regulations are considered lacking in this respect, then thought should be given to amendments so that the legislation can be brought to bear.

12.27 Lead Government Department: Business, Innovation and Skills

Recommendation 8

12.28 This report identifies the lack of substantive research in the area of novel psychoactive substances, which is crucial in making any informed decisions in relation to the status of any novel psychoactive substance. The ACMD appreciates this has been in part due to the speed at which NPS have surfaced in the UK and also due to the lack of funds for research at the present time. However, to ensure that the best possible advice is provided, concerted efforts need to be made to build on the research pool.

12.29 We applaud the Forensic Early Warning System developed by the Centre for Applied Science and Technology (CAST) which analyses test purchases of NPS, this builds on work done by academic units during 2009 and 2010 (Davies *et al*., 2010; Ramsey *et al*.,2010; Brandt *et al*, 2010a,b,c. Dargan et al 2010: Dargan PI, Hudson S, Ramsey J, Wood DM, The impact of changes in UK classification of the synthetic cannabinoid receptor agonists in 'Spice' International Journal of Drug Policy 2011;22:274-277). We encourage that funds are available through research councils for academic units to continue this activity. In addition there is an urgent need for provision of pure samples and reference materials of the various NPS for forensic science service providers to ensure accurate and reliable results for the analysis of both test purchase NPS samples and also biological samples from individuals presenting with acute toxicity related to the use of NPS.

12.30 So far there is limited provision for biochemical or pharmacological research on NPS's. This is important as it would provide rapid evidence of the profile of these substances in relation to existing psychoactive drugs and could therefore be used to predict the potential for harm associated with their use. The collaboration initiated with the National Institute of Mental Health Psychoactive Drug Screening Programme in the USA will help partly to fill this gap, but more biological/pharmacological, and social research is urgently needed, and could be achieved quickly and at relatively low cost.

12.31 Data collection on analytically confirmed cases of acute harm (toxicity) presenting to hospitals associated with the use of NPS is essential for informing decisions on the classification of these substances. Information on acute harm is currently collected on an ad hoc basis by a few specialist units in the UK and this has provided data from recent ACMD considerations of mephedrone and the cathinones, 'spice', GBL/1,4-BD, 1-BZP and other compounds. It is

important that resources are made available to increase data capture in this important area to enable ACMD and the government to be able to make decisions based on the actual harms associated with NPS.

12.32 **Recommendation: Provide resources for research on the chemistry, pharmacology, acute harm (toxicity) and social harms of novel psychoactive substances and encourage Business Innovation and Skills Department (BIS) and all research councils to put out calls in these areas.**

12.33 Lead Government Department: Home Office/Business, Innovation and Skills

Recommendation 9

12.34 The ACMD understands that the main method of promoting NPS is via the internet, where more often than not misleading claims are made about the substance, e.g. purporting that substances are bath salts or fish food. These terms are clearly used to legitimise the substances.

12.35 **<u>Recommendation</u>: Request the Advertising Standards Authority (ASA) to investigate claims made by NPS websites.**

12.36 Lead Government Department: Home Office

12.37 Recommendation: That a national system be implemented (by Trading or Local Authority Licensing) whereby all suppliers and potential suppliers or novel psychoactive substances are warned (by way of an official notice) that substances they sell **may** contain controlled substances. This will then put the onus on them as suppliers to ensure none of their products contain controlled substances.

Recommendation 11

12.38 The ACMD believes that education and awareness of NPS and associated skills development is crucial in relaying the message that although a substance may be legal it does not mean it is safe. Whilst providing information on potential harms of NPS is important and should be included within school-based drug awareness programmes, the changing nature of the NPS market means that developing health literacy and supporting healthy decision making around substances in general is also a useful long term goal. PSHE (Physical, Social and Health Education) provides an excellent framework for the delivery for such activities, and the findings of the current review of PSHE education should, in accordance with Ofsted recommendations, be used to promote consistency across schools in the provision of high quality, evidence-based substance use education.

12.39 The ACMD recommend building on local and European initiatives that are emerging, for example ReDNet.

12.40 The ACMD recommends that the government raise public awareness around NPS and implements strategies to reduce the demand for NPS by including NPS in substance misuse education in schools; developing targeted prevention initiatives and also treatment for those with acute problems (eg within A&E) and dependency. The following tools should be utilised to counter the prevalence of NPS;

1 Training

Training on NPS should be provided to young people and other services – both specialist and generic services Specialist substance misuse services

2 Monitoring

Better monitoring of NPS needs to be developed to ensure that new drugs and trends of use are identified as early as possible (see paragraph 12.22).

3 Information and advice for NPS users

Credible sources of information and advice need to be developed for young people taking NPS.

4 Wider public information

Care should be undertaken with the wider reporting and dissemination of information on NPS so as not inadvertently to encourage wider experimentation and use particularly among the under 16s. Education on the harms associated with NPS should specifically be delivered to young children in the latter stages of primary education so that they can be made aware that NPSs are highly likely to carry the same harms as controlled drugs of abuse.

12.41 Lead Government Department: Department for Education

Recommendation 12

12.42 There is clearly a need to share current practice, evaluate new treatment interventions and research `what works' in treating NPS dependence.

12.43 **Recommendation: That there should be investment by commissioners and health research bodies to enable them to collectively build evidence-based practice and disseminate this.**

12.44 Lead Government Department: Department of Health

Recommendation 13

12.45 **The ACMD recommends that demand reduction strategies should be developed including education, prevention and treatment interventions:**

- develop credible evidence-based public health messages on NPS to allow potential users to understand harms potential associated with NPS the choices they are making
- include NPS drug education in schools and targeting parents and ensure those delivering drugs education have current knowledge of NPS
- local areas develop evidence-based targeted prevention interventions for potential and new NPS users
- based on local needs assessments, develop treatment interventions to tackle acute NPS toxicity and NPS misuse and dependence, particularly develop competence in A&E services and young people and adult substance misuse services.

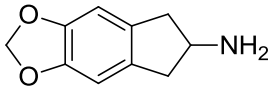
This requires national co-ordinated NPS knowledge and competency projects to keep abreast of emerging NPS and what are effective interventions – to inform public health messages, training and spread best practice in interventions.

12.46 Lead Government Department: Department of Health

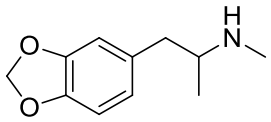
Annex A
An overview of the pharmacology of NPS

Cocaine or Amphetamine-like drugs
Many controlled drugs, although there may be chemical diversity, share a common mechanism of action in that they increase levels of brain monoamine chemical messengers by blocking their re-uptake after synaptic release. The monoamines involved are serotonin, *nor*-adrenaline and dopamine. The relative contributions of the individual monoamines to the stimulant/euphoric effects vary depending on the particular class of drug. All such drugs, to a varying degree, have additional actions, some of which may, especially at high doses, be manifested as adverse or toxic effects.

Controlled drugs possessing this mechanism of action include amphetamine, methylamphetamine, ecstasy (MDMA), and cocaine. Mephedrone and naphyrone (also known as NRG-1) which are amphetamine-like in their pharmacology and chemistry and which were widely advertised and used as legal highs, have now been added to the list of controlled drugs. Benzylpiperazine (BZP) with a mechanism of action more akin to that of MDMA is now banned in most countries. More recently desoxypipradrol, also a material with amphetamine-like effects was found to be the active principle in some samples of 'Ivory Wave', and has been made the subject of an import ban and control under the Misuse of Drugs Act 1971.



MDAI



MDMA

There are still other amphetamine-like legal highs readily available. One such is MDAI (methylenedioxy-aminoindane) promoted on websites as being capable of releasing serotonin without the undesirable neurotoxic effects of MDMA or the stimulant effects of amphetamine. Data on its pharmacodynamics and pharmacokinetics are limited and there are only anecdotal reports on its effects on users.

Dimethocaine (see above) is promoted on websites as a legal substitute for cocaine. Like cocaine, it acts as an anaesthetic, but it also inhibits the dopamine transporter in the brain and so reduces clearance of dopamine from the synaptic cleft and, from the limited information available on its pharmacology, it appears to be approximately equipotent with cocaine. But as yet it appears not to be widely used

LSD like drugs
Numerous tryptamine derivatives have been shown to have similar pharmacological actions as LSD-25. Two materials, alpha-methyltryptamine (AMT) and 5-methoxydiallyltryptamine (5-MeO-DALT)

are becoming more widely publicised by websites selling NPS. Both are currently outside the UK's generic controls on tryptamines and are therefore legally available. However, there is considerable overlap between the pharmacology of agents in this group and amphetamine-like drugs such that if members of this class of drugs had an action at certain serotonin receptors their pharmacology will then be LSD like. It is also possible to find agents that have a mixture of monoamine releasing and serotonin-receptor ligand activity.

Phencyclidine (PCP) and ketamine-like agents

Phencyclidine and ketamine were both initially developed as anaesthetic agents for human use but the use of phencyclidine was discontinued because of unacceptable side effects including hallucinations and psychotic reactions. However, ketamine is still used in paediatric care. Both continue to be used as veterinary anaesthetics. Both compounds have emerged as street drugs producing florid behavioural effects with a high incidence of 'bad trips'. The predominant pharmacological action is antagonist activity at central NMDA/glutamate receptors.

Both drugs are now controlled substances, as are some of the analogues of PCP, but other analogues including methoxetamine (a close analogue of ketamine) and the 3- and 4-methoxy derivatives of PCP are publicised on websites as legally available analogues. No information regarding their pharmacology or biochemistry is available but it would be surprising if they did not share the same activities and therefore have a potential to produce the same psychoactive effects as the parent compounds.

Annex B

Background – NPS in an Historical Context

This section illustrates in more detail some of the substances that have been used legally as intoxicants for many years, and reviews some of the more recent examples which have been reviewed by ACMD in the past few years. Alcohol, tobacco and caffeine are among the most widely used psychoactive drugs, but they do not form part of this review – which is focussed on substances which are controlled, or likely to be controlled under the Misuse of Drugs Act 1971

Nitrous Oxide

One of the earliest examples is nitrous oxide (N_2O), a colourless sweet-tasting gas, often referred to as "laughing gas" because of the sense of hilarity it may induce in users (Sheldin et al, 1993). First discovered by Joseph Priestley in 1772, its use was popularised by Humphrey Davy who inhaled the gas and reported its pain relieving and euphoric effects in 1784. Later the gas came into medical use as a useful anaesthetic for dental operations and other uses such as in childbirth where its short duration of action was an advantage (Becker and Rosenberg, 2008). Among the British upper classes "laughing gas parties" became popular in Victorian times; such parties also took place in the USA. Nitrous oxide still has widespread legitimate medical, dental and veterinary uses and has also found applications as a component of rocket fuel; a fuel additive; an aerosol dispersant; and in the catering industry in the dispensing of whipped cream. This latter use forms the basis for its legal sale by many web sites, in the form of small canisters or larger tanks, labelled for catering use – although clearly intended for recreational use. When inhaled the gas induces a brief period of euphoria which may be accompanied by "tears of joy". Users often wish to repeat their positive experiences with the gas, although there is no firm evidence of physical dependence. It appears to have few if any short term adverse effects, other than mild headache for some. Long term abuse can cause peripheral sensory neuropathies. Deaths linked to nitrous oxide are due to hypoxia replacement of oxygen with nitrous oxide (some of the deaths have also involved use of N_2O in an enclosed space which exacerbates hypoxia and/or in bags).

The recreational use of nitrous oxide has seen a sudden revival of interest in the 21st century, and it is now commonly available in certain clubs and at music festivals – where it is purchased in the form of gas-filled balloons. At the Glastonbury Festival in 2010, for example, it was reported that the ground was littered with discarded yellow balloons of this type.

The sale of nitrous oxide for catering or other legitimate commercial use is entirely legal, although its sale in forms such as gas-filled balloons clearly intended for human use violates the Medicines Act, and could be dealt with by MHRA – although there have been no prosecutions at Court. Five offenders have been arrested at the Glastonbury Festival over the last 2

years for supplying it for inhalation purposes and on the advice of the MHRA all have received Police Cautions.

Solvent abuse

A wide range of volatile materials can cause a temporary intoxication when the vapours are inhaled (Spurgeon, 2006). They include petrol, propane, butane, acetone and many others. These are present in hundreds of household products freely available over the counter at relatively low cost. Solvent abuse thus appeals to those who cannot afford or do not have access to other intoxicants. Children, teenagers and marginalised adults have traditionally been most likely to indulge in this behaviour. Solvents are inhaled from a soaked rag, or directly from an open container. Because the solvents are inhaled into the lungs, their effects are rapid in onset giving the desired "rush" of intoxication and euphoria, sometimes accompanied by hallucinations. Volatile substance abuse can also be undertaken in enclosed spaces and/or by inhalation from a bag which increases the risk of hypoxia and therefore the risk of complications and fatalities.

Repeated solvent use can have serious harmful effects, including liver and kidney damage, and in some cases death, usually from respiratory depression, inhalation of vomit, or cardiac arrhythmia. The popularity of solvent abuse was fuelled by its incorporation into pop culture in the 1970's. Some punk musicians, for example, glorified their use of solvent inhalation as a way of shocking the adult population. The growing number of solvent-induced deaths, particularly among children, however, led to the introduction of the Intoxicating Substances (Supply Act), 1985 which made it a criminal act to supply anyone under the age of 18 with a wide range of intoxicants. These include solvent-based glues, dry cleaning fluid, nail-varnish remover, lighter fuel refills, and a host of other materials. Manufacturers also responded by reducing the retail package size of products containing intoxicant solvents.

Although solvent abuse is still widespread, it has become far less prominent than it was 30-40 years ago, but deaths continue to occur – for example, there were 38 in the UK in 2008 and 46 in 2009. Volatile Substance associated deaths have been monitored by a programme at St Georges Hospital London (VSA reports).

'Poppers'

Poppers' are small bottles filled with volatile liquid chemicals called alkyl nitrites. Recreationally they are usually sniffed straight from the bottle, after breaking the sealed top, and they deliver a short, sharp high (Haverkos et al, 1994). Alkyl nitrites also relax smooth muscles including those surrounding blood vessels, thus increasing blood flow, and those around sphincters, thus facilitating intercourse. There are several variants in the alkyl nitrite group, including amyl nitrite, butyl nitrite and isobutyl nitrite.

Amyl nitrite is an active ingredient in licensed medicines, mainly for the treatment of cyanide poisoning. This is normally in the metallurgical industry where cyanide is used in activities involving gold, but there are a

few other circumstances where the product might be required. Any unlicensed product containing amyl nitrite is likely to fall within the definition of a medicinal product and, because it is unlicensed, be in breach of medicines regulations and therefore can be dealt with by MHRA. It is very unlikely that any 'poppers' on the UK market contain amyl nitrite.

Isobutyl or isopropyl nitrite esters are used as the active ingredients in 'poppers'. Neither substance is used as an active or excipient in any licensed medicine. Many varieties of colourfully packaged 'poppers' are freely sold at music festivals and in high street 'head shops'. They are relatively cheap and appeal to young people looking for a short-lasting high. 'Poppers' are normally marketed by manufacturers or importers as "room-odouriser". Retailers often describe them as aromas. They are sold under brand names such as GOLD, RAVE, REDS and many others, mainly from sex shops (their effects are said to enhance sexual pleasure) or "head shops" selling alternative life-style products - not from home-ware shelves in mainstream supermarket chains. 'Poppers' are often sold in gay nightclubs and also in head shops.

'Poppers' would appear to fall within the scope of 'The Intoxicating Substances (Supply) Act 1985' and, as there is evidence that 'poppers' are being sold to minors in retail outlets around the country, it would seem sensible that they should be dealt with using this legislation.

Trading Standards Departments (BIS) are responsible for the enforcement of the relevant legislation.

'Poppers' are not subject to the controls of the Misuse of Drugs Act 1971 and there are no plans to bring them under the control of the 1971 Act as, at present – unlike other substances of abuse – their misuse, within the terms of section 1 of the Act, is not seen to be capable of having "harmful effects sufficient to constitute a societal problem". There have been a small number of deaths from their use. The ACMD is also aware that the use of 'poppers' can lead to methaemoglobinaemia in users. Methaemoglobinaemia may cause significant tissue hypoxia, leading to severe, potentially life-threatening clinical features and/or death (Hunter L, Gordge L, Dargan P, Wood DM. Methaemoglobinaemia associated with the use of cocaine and volatile nitrites as recreational drugs: a review. British Journal of Clinical Pharmacology 2011; 72:18-26.)

As sniffing isobutyl nitrite causes a physiological effect, the MCA (Medicines Control Agency) (as was; now Medicines and Healthcare products Regulatory Agency (MHRA)) brought a prosecution in 1999. This was on the basis that 'Poppers' containing isobutyl nitrite were medicines and hence required a product licence for sale and supply in the UK. The company brought to trial (QUIETLYNN who manufactured and supplied these products) and its directors – were subsequently found not guilty. It is understood that there was sufficient argument by the defence that these products did not cause significant harm. An appeal was considered but not pursued and the status of the products has remained under review since

then. No further prosecutions have been attempted as there was no material change to the products' ingredients. In addition, since the court case, companies have been very careful to keep the description of products to 'room odourisers' and this is reflected in the instructions for use.

The introduction of The Dangerous Substances and Preparations (Safety) Regulations 2006 has altered the status of certain 'poppers' products. The legislation which is enforced by the Department for Business, Innovation and Skills (BIS), prohibits the supply of isobutyl nitrite, as it has been classified as a carcinogen, As a result, the use of isobutyl nitrite in 'poppers' is effectively banned. Therefore, products manufactured and sold containing this substance are in breach of regulatory requirements and could be dealt with by Trading Standards Departments using powers drawn from the Consumer Protection Act 1987. Further the ACMD are aware of risks associated with nitrites as they can be highly flammable with potential for harm related to burns if they are used by smokers.

Manufacturers and distributors, however, in recognition of the ban on isobutyl nitrite, have substituted isopropyl nitrite as the active ingredient. It is likely that that this will have a similar physiological effect to isobutyl nitrite. This provides an early example of how small changes in the chemical formulae of products can be used to avoid the law.

Plants and fungi

A number of natural species contain psychoactive chemicals, and fresh or preserved plant and fungal materials have long been offered for sale via 'head shops' and internet outlets. The legal position regarding such natural materials is complex, a situation which, in the early part of this century, a number of distributors made use of to enable them to conduct large-scale and overt marketing of non-native mushroom species containing hallucinogens ("magic mushrooms"). This activity was largely terminated by the Drugs Act 2005, which controlled "fungus (of any kind) which contains psilocin or an ester of psilocin". However, other natural materials, such as *Salvia divinorum* and 'Fly Agaric' mushrooms, which contain other psychoactive chemicals, remain on sale.

Any preparations containing controlled drugs are controlled under the Misuse of Drugs Act 1971, and this includes plant materials if there is evidence of the material being prepared 'by the hand of man' (there is a large amount of case law on this topic mostly relating to *Psilocybe* mushrooms prior to the Drugs Act 2005).

A recent attempt to prosecute for supply of dried cacti containing mescaline (R v Sette, 2007) was struck down on the basis that, as hallucinogenic cacti weren't specifically addressed in the 2005 Drugs Act, their legal position remained too obscure to permit a prosecution to proceed.

1-Benzylpiperazine (BZP)

1-Benzylperazine (BZP) is a synthetic drug prepared from piperazine, an antihelminthic medicine used to control intestinal roundworms. Piperazine itself has no psychoactive properties, but BZP acts as an amphetamine-like psychostimulant. Laboratory animals are unable to distinguish the subjective effects of BZP from those induced by cocaine or amphetamine in drug discrimination tests. In recreational use the human dose of BZP is usually 100mg taken orally as a tablet or powder (EMCDDA Risk Assessment,)

The recreational use of BZP first became popular in New Zealand, where for a period of several years from 2000 it was widely available as a legal "party drug". BZP was freely available over the counter in many shops and sold under a variety of brand names. Manufacturers formed the "New Zealand Social Tonics Association" with its own code of practice to ensure the maintenance of quality standards. The New Zealand Government placed BZP into a new "Class D", under which, like alcohol and tobacco, its sale was restricted to adults. This social experiment terminated in 2008, when the New Zealand Government made BZP illegal under their Misuse of Drugs Act.

By the early years of this century BZP and some related chemical analogues, claimed to be more ecstasy-like in their profiles, became legally available in Europe. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) conducted a risk assessment of BZP in 2007 and concluded that its sale in Europe should be controlled. In 2007 the UK MHRA issued a notice that the sale of BZP as a product for human use was illegal, and ACMD conducted its own review of the evidence and recommended that BZP and various derivatives should be made illegal as Class C substances under the MDA (ACMD:1-Benzylpiperazine Report, 2008) – this was accepted and enacted into law in December 2009.

There seems little current interest in BZP as a product but recent Police seizures show that users and dealers alike are mistakenly selling and using BZP or the related drug trifluoromethyl-phenyl-piperazine (TFMP) in the belief that it is Ecstasy. Nationally, Police seize far more Piperazines than Ecstasy.

There have been a total of 36 deaths in which BZP has been implicated, usually in conjunction with alcohol (National Programme on Substance Related Deaths [npSAD] 2011).

GHB and its analogues GBL and 1,4-butanediol

Gamma-butyrolactone (GBL) and the related substance 1,4-butanediol (1,4-BD) are colourless liquids widely used in the chemical industry as solvents or precursors for plastics manufacture. They are also present in a variety of domestic products as solvents, for example as nail-polish remover or for cleaning oily machinery. It is estimated that the UK chemical industry imports 1000 tons of GBL and 5000 tons of 1,4-BD annually.

Both substances are rapidly metabolised in the human body to form gamma-hydroxybutyrate (GHB). GHB acts as an intoxicant, and was reviewed some years ago by ACMD, culminating in a recommendation in 2003 that it be banned under the MDA as a Class C substance. More recently GBL was recognised as representing a legal loophole, legally available but converted within a few minutes after ingestion to the banned substance GHB. Until recently pure GBL could be purchased from various internet retailers in amounts up to 10 litres. A 250 ml bottle, for example, could be purchased for £20. Since the human intoxicant dose is approximately 1ml, this was equivalent to 250 human doses, at a unit price of 8p. Not surprisingly, the use of GBL as a cheap intoxicant grew, particularly in the club scene. GBL induces a rapid intoxication and euphoria, accompanied by a loss of inhibitions. Unfortunately, the dose-response is fairly steep and somewhat higher doses can lead to sedation and sleep, and in overdose to coma, hypothermia and bradycardia – sometimes culminating in death. The npSAD has identified at least 96 deaths in the UK since 1995 in which GBL/GHB were associated (the rapid metabolism of GBL makes its detection in body fluids or tissue impossible); at least 22 of these involved GBL (np-SAD, 2011). Although there is no direct evidence, GBL has been implicated in drug-assisted sexual assault, There is increasing evidence that the repeated use of GHB or GBL are is capable of inducing dependence

ACMD reviewed the evidence for GBL and 1,4-BD misuse and recommended that both substances be brought under the MDA (ACMD 2008 GBL & 1, 4-BD: Assessment of risk to the individual and communities in the UK). This advice was implemented in December 2009. However, because of the important industrial and commercial uses of these substances exemptions had to be made for these uses and their classification as Class C drugs represents only a limited means of control. How effective the legal banning of GBL and 1,4-BD under the MDA has been remains to be seen. The rise in the popularity of GBL provides another illustration of how small changes in chemistry can yield substances that avoid legal bans.

More than a hundred deaths have been attributed to GHB/GBL (national programme for substance abuse deaths 2011).

Synthetic cannabinoid receptor agonists – 'Spice'

In the early years of the century a novel psychoactive substance product was marketed by internet retail sites and high street "head shops" under the product name "Spice". It was imported from China and claimed to be a smoking mixture composed of various herbs. The product was attractively packed in silver or gold foil sachets and modestly priced at £10-20.

Users discovered that smoking this product had an intoxicant effect remarkably similar to that induced by smoking illegal cannabis, and this information spread rapidly through user internet sites. The popularity of "Spice" was at first mysterious, since numerous other herbal products previously claiming to act as novel psychoactive substances had usually

proved disappointingly ineffective. It was a brilliant piece of analytical detective work by a German forensic laboratory that first revealed the truth. The herbal mixture in the product had been laced with small quantities of synthetic chemicals that acted on the cannabinoid receptor in the brain to simulate the actions of natural cannabis.

During the 1970s, following the discovery of Δ9- tetrahydrocannabinol (THC) - as the principal psychoactive ingredient in herbal cannabis, the pharmaceutical industry generated numerous synthetic cannabis-like chemicals with the goal of separating the medical benefits of cannabis from its intoxicant actions. This venture proved unsuccessful and was abandoned, but detailed reports of hundreds of different synthetic cannabinoids remained in the scientific literature (Makriyannis and Rapaka, 1990; Iversen, 2008a). Thirty years later this literature was rediscovered and a range of different synthetic cannabinoids were synthesised to add to the "Spice" product. Some of these substances are more than a hundred times more potent than cannabis itself, so only minute amounts had to be added to the herbal product – making their analytical detection extremely difficult. This was compounded by the use of several different synthetic cannabinoids in different batches of 'Spice'.

The ACMD reviewed this issue and concluded that although little detailed information was available on the pharmacology or harmfulness of these compounds, they could be assumed to carry the same properties and to possess harmfulness commensurate with that of cannabis – which had been thoroughly reviewed previously. This 'argument by analogy' was to prove valuable in other contexts as novel psychoactive substances emerged. ACMD made an extensive recommendation for a chemical generic ban covering virtually all known synthetic cannabinoids, in five distinct chemical classes, recommending that they be made Class B drugs under the MDA (ACMD Report: Consideration of the Major Cannabinoid Agonists, 2008). These recommendations were accepted and passed into law in December 2009. In light of the identifications of substances such as RCS-4 and AM-694 by the HO-CAST Forensic Early Warning System, it is clear that loopholes have already been found and these substances are legally available. The use of synthetic cannabinoids in this product illustrates the increasing sophistication of the chemists responsible, who mined the scientific literature to obtain information on the synthetic cannabinoids published by academic and pharmaceutical laboratories in the 1970s. Further there is published evidence that products containing synthetic cannabinoids remain widely available that newer synthetic cannabinoid receptor agonists that fall outside the legislation are also now available (Dargan PI, Hudson S, Ramsey J, Wood DM. The impact of changes in UK classification of the synthetic cannabinoid receptor agonists in 'Spice').

Ecstasy

The psychoactive effects of this substance (3,4-methylenedioxy-methamphetamine or MDMA) were first reported by the American chemist Alexander Shulgin in the 1960s. It became popular as a "party drug" in the

USA and later in Europe because of its unique ability to act both as an amphetamine-like stimulant and as an “empathogen” – causing users to feel socially relaxed and euphoric. MDMA was also widely used as an aid to psychotherapy by psychiatrists, particularly in the USA. Its use as a recreational drug took off as part of the “rave dance” culture in the USA and Europe during the 1980s, and it continues to be widely used despite legal bans (Iversen 2008b).

In Britain MDMA was made illegal in 1977 under the Misuse of Drugs Act 1971 – and was given a “Class A” status – which it continues to retain. Despite the severe penalties potentially associated with possession or dealing in Class A drugs, MDMA continues to be widely used. According to the British Crime Survey approximately 250,000 young people, aged 16-24, and some 40,000 admit to being regular users – although in this case regular usually means “at weekends” rather than every day. ACMD undertook a detailed review of the use of MDMA and the harms associated with it (ACMD: MDMA (Ecstasy): A Review of its Harms and Classification under the Misuse of Drugs Act 1971, 2008). The review concluded that the medical and societal harms of MDMA were not commensurate with its Class A status, and recommended that it be downgraded to Class B. The Home Secretary, however, did not accept this recommendation.

By the time ecstasy became popular in the UK in the late 1980s, it was already a Class A controlled drug, by virtue of the generic controls placed on phenethylamines in 1977 in response to the appearance of other psychoactive phenethylamines such as DOB (2,5-Dimethoxy-4-bromamphetamine) and STP (2,5-Dimethoxy-4-methylamphetamine). As stated under BZP (para 2.16 above) the majority of "ecstasy tablet" users are in fact taking BZP, but over the last 2 years there have been significant increases in the use of Crystal Ecstasy a much more potent form of the drug.

In the USA MDMA was legally available until banned as a Schedule 1 drug in 1985. In Britain MDMA was available legally until 1977 – but curiously its widespread use occurred after it was made illegal.

Cathinones

(i) mephedrone

This is also a wholly synthetic chemical, sometimes referred as the first “internet drug”. Mephedrone was a 'designer drug' in that it was specifically designed as a Novel Psychoactive Substance that had not previously been reported in the literature. The rapid spread of availability and use of this cathinone derivative psychostimulant in the UK was dramatic during the latter half of 2009 and in the first quarter of 2010. Mephedrone (4’-methyl-methcathinone) is a chemical derivative of the naturally occurring amphetamine-like substance cathinone – the active ingredient in the shrub khat (*Catha edulis*). Whereas herbal khat has not so far been a controlled product, cathinone has long been banned under the MDA as a Class C substance. It acts as a weak form of amphetamine. Mephedrone is more potent than cathinone and its intoxicant effects combine the stimulant

properties of amphetamine with the empathogenic profile of MDMA (EMCDDA Drug Profiles).

The reported dose by users of mephedrone is around 50-100mg, usually taken orally, but sometimes insufflated into the nose. In rare instances it has been intravenously injected. The easy availability of mephedrone through the internet led to many young people who had never previously used illegal drugs to experiment with it. It is also possible that some long term cocaine users, disappointed by the poor quality of street cocaine, were attracted to a legal product which – at least initially – lived up to the purity standards claimed (>98%). Use was spread rapidly through internet social network sites, aided also by press and television coverage. Supplies of kilogram amounts could be obtained fairly cheaply from internet suppliers (1kg for £2000 - @10-20p per human dose). Users may have been seduced into thinking that "it is safe because it is legal". Typically during an evening out, users would dose repeatedly and use their entire supply of approximately 1g.

Since mephedrone and related compounds were described by internet retailers as "plant food" or "fish food" and clearly indicated as "NOT FOR HUMAN CONSUMPTION" they appeared to be immune from regulation under Trades Description or Medicines Act legislation – although this has never been challenged.

The ACMD first became aware of this novel psychoactive substance in July 2009 from seizures at a music festival on the Isle of Wight. Monitoring its rapid rise in use in the UK, ACMD alerted the then Home Secretary in December 2009 of the possible dangers of this substance, and launched a risk assessment. As in the case of the synthetic cannabinoids, little published scientific information was available on mephedrone, so ACMD had to argue largely by analogy with amphetamines – on the grounds that the cathinones are closely related chemically and in their actions. Although little was known of the long-term harms caused by mephedrone, the harmfulness of the classical amphetamines was well documented. This resulted in the submission of a detailed report in March 2010 with the recommendation of an immediate import ban, and that mephedrone, together with a broad range of related cathinones derivatives, be banned under the MDA as Class B substances (ACMD- : Consideration of the Cathinones, 2010). A number of bodies such as the National Poisons Information Service, Guy's and St Thomas' NHS Foundation Trust and other clinicians/scientists provided data that demonstrated the potential for toxicity associated with the use of Mephedrone. There has been some confusion over names 'Mephedrone', 'Methadone' and 'Methedrone', especially at the early stages of Mephedrone emergence in the UK, there may have been some mis-recording of Mephedrone presentations at A&Es where at times it was being recorded as Methadone toxicity. The acute toxicity was used to inform the decision made to classify it. This recommendation was rapidly accepted and turned into law in April 2010 (ACMD, 2010). Details of the npSAd report on mephedrone associated deaths are provided in Section 9 below.

(ii) Naphthylpyrovalerone (Naphyrone)

Despite the broad chemical generic ban on psychoactive cathinones imposed in April 2010, suppliers were able to find some loopholes, and within days a naphthyl derivative, Naphthylpyrovalerone (commonly referred as NRG-1) which lay outside the generic scope was offered for sale by internet retailers – advertised as "the legal alternative to mephedrone". ACMD considered this case urgently, arguing again by analogy with the known amphetamines together with some neurochemical properties of the substance which had been published – placing it in the category of cocaine/amphetamine-like substances. ACMD recommended that Naphthylpyrovalerone and related chemical analogues be banned under the MDA as Class B drugs, and this was accepted and enacted into law in mid-2010. (ACMD: Consideration of the naphthylpyrovalerone analogues and related compounds*,* 2010). There are at least two cases in which naphyrone has caused or contributed to death (np-SAD).

The cathinones illustrated the speed with which Novel Psychoactive Substances can become available and used – and the rapidity of the suppliers' reaction to the initial ban – almost immediately finding legal loopholes to exploit. We must expect this to happen again on future occasions.

Desoxypipradrol

During 2010 a new Novel Psychoactive product 'Ivory Wave' began to be advertised on internet sites and became more widely used, following the ban on cathinones. This time the retailers failed to disclose the active psychoactive ingredient(s), stating that the product should be used as "bath salts" and that it contained 'Epsom salts, bicarbonate of soda and natural amino acids'. Analysis of test purchases, however, initially revealed the active ingredient to be methylenedioxypyrovalerone (MPDV) – one of the banned cathinone derivates. Subsequent purchases, however, revealed a different psychoactive ingredient – desoxypipradrol. The Home Office Centre for Applied Science and Technology Forensic Early Warning System found that desoxypipradrol was also identified in a purchase from a head shop in Edinburgh in March 2011 under the product name 'Lunar Wave'.

Desoxypipradrol is not controlled and is closely related chemically to the Class B drug methyl phenidate (®Ritalin) – an amphetamine-like psychostimulant used in treating Attention Deficit Hyperactivity Disorder (ADHD) in children. The ACMD began an investigation of this new product in mid-2010 and heard reports of users admitted to hospital A&E units with persistent severe agitation, sometimes lasting for several days, often accompanied by psychosis. These effects were consistent with the properties of desoxypipradrol, as an amphetamine-like drug. After consideration of the reports of the harmfulness of this new product, the ACMD recommended that the Home Secretary impose an immediate ban on the import of desoxypipradrol (under the Open General Import Licence), and this was promptly acted upon (ACMD, 2010). There are two cases

awaiting inquest in which desoxypipradrol is believed to have caused or contributed to death in the summer of 2010, as well as several deaths in which MDPV was detected (np-SAD). The ACMD undertook a further detailed analysis of desoxypipradrol and recommended to the Home Secretary that it be controlled under the Misuse of Drugs Act 1971 (ACMD, 2011).

Annex C: Reporting of drug-related deaths.

Established in 1997, and sponsored by the Department of Health, the National Programme on Substance Abuse Deaths (np-SAD) regularly receives notifications on a voluntary basis from coroners and other sources across the UK and Islands when inquests and other formal investigations into drug-related deaths or deaths of individuals with a history of drug use have been completed. This information is collated, analysed and disseminated in several ways: annual reports on drug-related deaths in the UK; contributions to the annual reports of the UK Focal Point, the European Monitoring Centre for Drugs and Drug Addiction, and United Nations; academic papers; information to local Drug and Alcohol Action Teams (DAATs) and to Primary Care Trusts.

np-SAD Contribution to UK Early Warning System

In addition to its routine surveillance activities, the Programme also provides real-time information on the emergence of novel substances or new ways of taking existing substances to the UK Early Warning System and the Advisory Council on the Misuse of Drugs (ACMD). This information comes both from notifications of deaths and from 'alerts' or other information provided by the various agencies and networks, national and international, with which the Programme maintains contacts. Through these channels (including coroners, forensic toxicologists, DAATs, and the Scottish Crime & Drug Enforcement Agency), the Programme became aware of the emerging issue of the use of various synthetic cathinones and similar substances, and of their potential adverse health consequences. It was decided to take a pro-active approach to monitor the situation especially in respect of the potential role of these new substances in causing or contributing to death.

Provision of information to the ACMD

The np-SAD provided information to the ACMD for its consideration of mephedrone and other cathinones. This information was included in the ACMD's report to the Home Secretary at the end of March 2010. Regular updates have been provided to the ACMD Secretariat. The present update was invited by the Chair of the ACMD Working Group on "Novel Psychoactive Substances" to provide a summary of what the np-SAD understands is the current situation. Unfortunately, Department of Health funding for this programme was terminated in August 2010, depriving ACMD of continuing input on the rapidly changing figures on drug-associated deaths. The Office for National Statistics can provide some information, but on a much slower time frame, on a different counting basis, and only for England & Wales. The ACMD have made representations to the Department of Health of the importance of this programme in informing on the harmfulness of drugs old and new, and hope that the evidence can still be collected.

The following information on suspected drug deaths involving mephedrone is the situation as known on 20 October 2011 (see annex c table 1) and serves as an example of np-SAD input. A number of limitations need to be

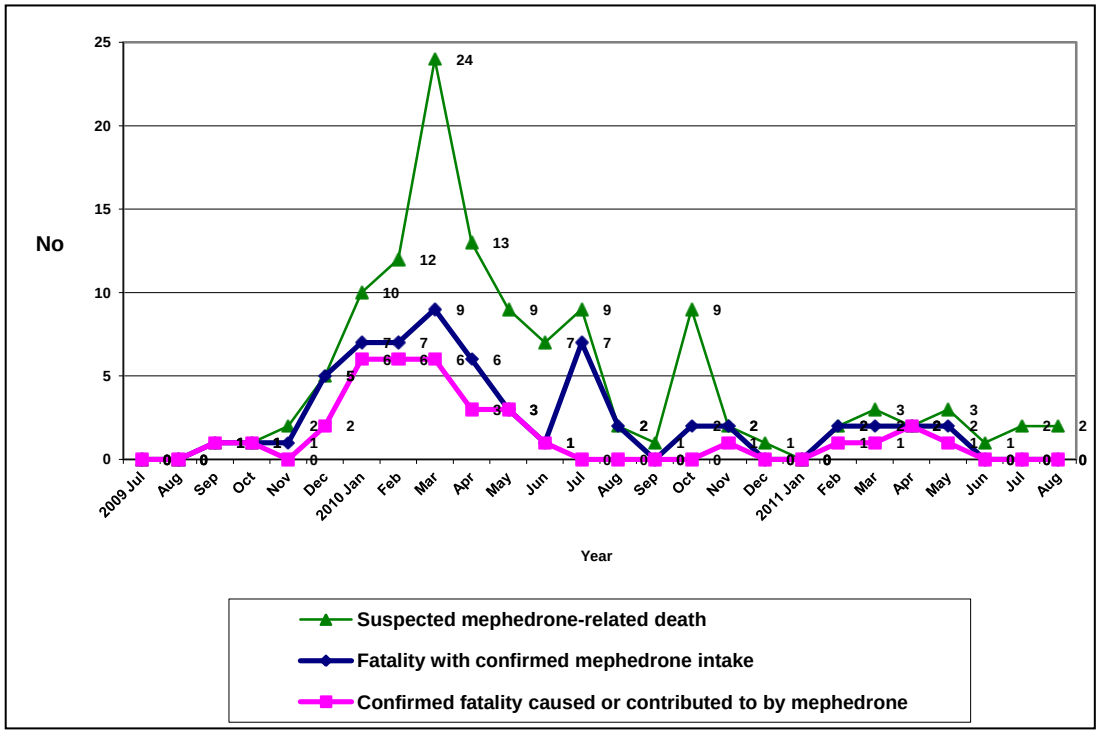
borne in mind: (a) remaining 'positive' cases are awaiting further inquiries or inquest; (b) not all suspected cases may have been identified; several deaths have been reported for which the inquests have yet not been completed; (c) the fact that mephedrone may have been involved in death cannot be confirmed until the relevant coroner or Procurator Fiscal has concluded her/his inquest or other formal inquiry; and (d) the presence of mephedrone in post mortem toxicology does not necessarily imply that it caused or contributed to a death.

Table 1: Number of suspected and confirmed cases of mephedrone-related deaths, UK and Islands, as at 20 October 2011

Region	No of suspected cases	No of cases with completed legal process	No of cases positive for mephedrone	No of cases negative for mephedrone	No of cases awaiting toxicology results	No of confirmed cases where mephedrone caused/ contributed to death
England	95	45	66	20 (but several positive for other methcathinones)	9	29 (5 forms awaited)
Wales	4	1	4	0	0	1
Scotland	16	9	12	3	1	6
Northern Ireland	9	6	4	2	3	3
Guernsey	2	2	1	2	0	2
Jersey	0	0	0	0	0	0
Isle of Man	1	1	1	0	0	1 (form awaited)
Total	127	64	88	29	13	42 (6 forms awaited)
Notes: The toxicology results for some suspected cases still remain to be ascertained						

The evolution of cases with toxicology positive for mephedrone and deaths where the substance has been confirmed as causing or contributing to death is shown in the following figure. There are some cases for which information is not yet available.

Figure 1: Evolution of cases with confirmed positive toxicology for mephedrone, based on returned np-SAD forms as of 20 October 2011



According to press and media reports, there are concerns by parents of young people who appear to have committed suicide, typically by hanging, that mephedrone may have contributed to them feeling low or depressed. At least 19 inquests have concluded such a link. These reports come from all parts of the UK. In these cases, mephedrone appears to act in similar ways to cocaine, MDMA and amphetamine. np-SAD has recorded 14 deaths from hanging following the consumption of these substances.

References

1. Advisory Council on the Misuse of Drugs. *Advice on 'Ivory Wave'* Home Office, London, 2010. Also available at homeoffice.gov.uk

2. Advisory Council on the Misuse of Drugs. *Consideration of the Cathinones.* Home Office, 2010. Also available at homeoffice.gov.uk

3. Advisory Council on the Misuse of Drugs. *Consideration of the naphthylpyrovalerone analogues and related compounds.* Home Office, London, 2010. Also available at homeoffice.gov.uk

4. Advisory Council on the Misuse of Drugs. *Consideration of the major cannabinoids agonists.* Home Office, London, 2009. Also available at homeoffice.gov.uk

5. Advisory Council on the Misuse of Drugs. *GBL & 1,4-BD: Assessment of risk to the individual and communities in the UK*. Home Office, London, 2008. Also at homeoffice.gov.uk

6. Advisory Council on the Misuse of Drugs. *MDMA ('ecstasy'): a review of its harms and classification under the Misuse of Drugs Act 1971.* Home Office, London, 2008. Also available at http://www.homeoffice.gov.uk/publications/alcohol-drugs/drugs/acmd1/mdma-report?view=Binary

7. Advisory Council on the Misuse of Drugs. *Control of 1-benzylpiperazine (BZP) and related compounds*. Home Office, London, 2008. Also available at homeoffice.gov.uk

8. Brandt SD, Sumnall HR, Measham F, Cole J. (2010b); Analyses of second-generation 'legal highs' in the UK: initial findings. Drug Test Analysis 2:377-382

9. Brandt SD, Sumnall HR, Measham F, Cole J. (2010a); Second generation mephedrone. The confusing case of NRG-1. British Medical Journal 341:c3564

10. Brandt SD, Freeman S, Sumnall HR, Measham F, Cole J. (2010c); Analysis of NRG 'legal highs' in the UK: identification and formation of novel cathinones. Drug Test Analysis. [Epub ahead of print, PMID: 21191917]

11. Becker DE, Rosenberg M, (2008); Nitrous Oxide and the Inhalation Anaesthetics. Anesthesia progress. 55: 124–131.

12. Brennan I., Moore S.C., Byrne E. et al. Addiction: 2011, 106, p. 706–713

13. Centers for Disease Control and Prevention (CDC). (2011); Emergency department visits after use of a drug sold as "bath salts"--Michigan, November 13, 2010-March 31, 2011. MMWR Morbidity and Mortality Weekly Report 60:624-7.

14. Dargan PI, Button J, Hawkins L, Archer JR, Ovaska H, Lidder S, Ramsey J, Holt D, Wood DM. (2008); Detection of the pharmaceutical agent 'Glaucine' as a recreational drug. European Journal of Clinical Pharmacology 64:553-554.

15. Dargan PI, Hudson S, Ramsey J, Wood DM. The impact of changes in UK classification of the synthetic cannabinoid receptor agonists in 'Spice' International Journal of Drug Policy 2011;22:274-277.

16. Davies S, Wood DM, Smith G, Button J, Ramsey J, Holt DW, Dargan PI, (2010); Purchasing "Legal Highs" on the Internet – Is there consistency in what you get? Quarterly Journal of Medicine 103:489-493.

17. Davies S, Lee T, Ramsey J, Dargan PI, Wood DM. Risk of caffeine toxicity associated with the use of "legal highs" (novel psychoactive substances). European Journal of Clinical Pharmacology 2011 – In Press.

18. Derungs A, Schietzel S, Meyer MR, Maurer HH, Kr Henb Hl S, Liechti ME. (2011); Sympathomimetic toxicity in a case of analytically confirmed recreational use of naphyrone (naphthylpyrovalerone). Clinical Toxicology (Philadelphia) Jul 8. [Epub ahead of print] PMID: 21740148.

19. European Monitoring Centre for Drugs and Drug Addiction. Risk Assessment of BZP in the Framework of the Council Decision: EMCDDA Risk Assessments 2009

20. Gee P, Jerram T, Bowie D. (2010); Multiorgan failure from 1-benzylpiperazine ingestion--legal high or lethal high? Clinical Toxicology (Philadelphia) 48:230-3.

21. Gee P, Jackson S, Easton J. (2010); Another bitter pill: a case of toxicity from DMAA party pills. New Zealand Medical Journal 123:124-7.

22. Gee P, Gilbert M, Richardson S, Moore G, Paterson S, Graham P. (2008); Toxicity from the recreational use of 1-benzylpiperazine. Clinical Toxicology (Philadelphia) 46:802-7.

23. Guidance Note 8, A guide to what is a medicinal product. www.mhra .gov.uk/home/group/is-lic/document/publication/con007544.pdf

24. Haverkos HW, Kopstein AN, Wilson H. and Drotman P. (1994); Nitrite inhalants: history, epidemiology, and possible links to AIDS, Environmental Health Perspectives. 102: 858–861.

25. Hudson S, Ramsey J, King L, Timbers S, Maynard S, Dargan PI, Wood DM. The use of high resolution accurate mass spectrometry to detect reported and previously un-reported cannabinomimetics in 'Herbal High' products. Journal of Analytical Toxicology 2010;34(5):252-260.

26. Hudson S, Ramsey J. The emergence and analysis of synthetic cannabinoids. Drug Test Anal 2011;3:466-78.

27. Hunter L, Gordge L, Dargan P, Wood DM. Methaemoglobinaemia associated with the use of cocaine and volatile nitrites as recreational drugs: a review. British Journal of Clinical Pharmacology 2011;72:18-26.

28. IPPT20050609,ECJ, HLH Warenvertriebs – Orthica v Deutschland

29. Iversen, LL (2008a); "The Science of Marijuana, Second Edition", Oxford University Press, New York

30. Iversen LL. (2008b); "Speed, Ecstasy, Ritalin: the Science of Amphetamines", Oxford University Press, Oxford

31. James D, Adams RD, Spears R, Cooper G, Lupton DJ, Thompson JP, Thomas SH. (2010); on behalf of the National Poisons Information Service. Clinical characteristics of mephedrone toxicity reported to the UK National Poisons Information Service. Emergency Medicine Journal [Epub ahead of print] PMID: 20798084.

32. Kendall S, Rodger J, Palmer H. (2010) Redesigning provision for families with multiple problems: early impact and evidence of local approaches. Research Report DFE-RR046. Department for Education.

33. Lidder S, Dargan PI, Button J, Ramsey J, Holt DW, Wood DM. (2008); Cardiovascular toxicity associated with recreational use of diphenylprolinol (diphenyl-2-pyrrolidinemethanol (D2PM)) Journal of Medical Toxicology 4:167-9.

34. Makriyannis A, Rapaka R. (1990); The molecular basis of cannabinoid activity. Life Sciences, 47:2173-2184.

35. McCarron MM, Schulze BW, Thompson GA, Conder MC, Goetz WA. (1981); Acute phencyclidine intoxication: incidence of clinical findings in 1,000 cases. Ann Emergency Medicine; 10: 237-242.

36. Measham F. 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 (4), pp.437-464.

37. Measham, F., Wood, D., Dargan, P. and Moore, K. (2011), The Rise in Legal Highs: Prevalence and patterns in the use of illegal drugs and first and second generation 'legal highs' in south London gay dance clubs, *Journal of Substance Use*, 16 (4): 263-272.

38. Measham, F., Moore, K and Østergaard, J. (2011), *Emerging Drug Trends in Lancashire: Night Time Economy Surveys. Phase One Report,* Lancaster: Lancaster University and Lancashire Drug and Alcohol Action Team, pp.1-62. Available at: http://www.ldaat.org/files/emerging_trends_report.pdf

39. Measham, F., Moore, K. and Østergaard, J. (2011), Mephedrone, 'Bubble' and Unidentified White Powders: The contested identities of synthetic 'legal highs', *Drugs and Alcohol Today*, 11 (3): 137-147.

40. Mixmag (2010). Mixmag Drugs Survey. February: 225: 44-53.

41. Mixmag (2011). The 2011 Drugs Survey. March: 238: 49-59.

42. Morgan CJ, Curran HV. (2011); the Independent Scientific Committee on Drugs (ISCD). Ketamine use: a review. Addiction ; (In Press).

43. Moore K, Wood DM, Dargan PI, Measham F. (2001); The Rise in Legal Highs: Prevalence and patterns of illegal drug and 'legal high' use in south London gay dance clubs. Journal of Substance Use 2011;16:263-72

44. Ovaska H, Viljoen A, Puchnarewicz M, Button J, Ramsey J, Holt DW, Dargan PI, Wood DM. (2008); First case report of recreational use of 2,5-dimethoxy-4-chloroamphetamine (DOC) confirmed by toxicological screening. European Journal of Emergency Medicine 15:354-6.

45. Personne M, Hulten P. (2008); Bromo-Dragonfly: a life threatening designer drug. Clinical Toxicology (Philadelphia); 46: 379-380.

46. Regan L, Mitchelson M, Macdonald C. (2010); Mephedrone toxicity in a Scottish emergency department. Emergency Medical Journal. [Epub ahead of print] PMID: 21183522.

47. Ramsey J, Dargan PI, Smyllie M, Davies S, Button J, Holt DW, Wood DM. (2010); Buying 'legal' recreational drugs does not mean

that you are not breaking the law. Quarterly Journal of Medicine. 103:777-783.

48. Sammler EM, Foley PL, Lauder GD, Wilson SJ, Goudie AR, O'Riordan JI. (2010); A harmless high? Lancet 376:742.

49. Shah AD, Wood DM, Dargan PI. (2011); Survey of ICD-10 coding of hospital admissions in the UK due to recreational drug toxicity. Quarterly Journal of Medicine (QJM) [Epub ahead of print; doi: 10.1093/qjmed/hcr074].

50. Sheldin, M, Wallechinsky, D, Salver S., (1993);"Laughing Gas", Ronin Publishing, PMCID: PMC1472097

51. Shulgin A and Shulgin A. (1997); "TIHKAL The Continuation", Transform Press, Berkeley, CA: 437-441.

52. Serious Organised Crime Agency (Intelligence Report). 2011. Drugs: Risks Associated with New Psychoactive Substances.

53. Smith K, Flatley J. (2011); Drug Misuse Use Declared, Findings from the 2010/11, British Crime Survey; HOSB: 12/11

54. Spurgeon A. (2006);"Watching Paint Dry: Organic Solvent Syndrome in late- Twentieth-Century Britain", Medical History. 50(2): 167–188.

55. Thorlacius K, Borna C, Personne M. (2008); Bromo-dragon fly - life-threatening drug. Can cause tissue necrosis as demonstrated by the first described case. Lakartidningen; 105: 199-200.

56. Wood DM, Dargan PI, Button JS, Holt DW, Ovaska H, Ramsey J, Jones AL. (2007); Collapse, reported seizure - and an unexpected pill. Lancet; 369:1490

57. Wood DM, Button J, Lidder S, Ramsey J, Holt DW, Dargan PI.(2008a); Dissociative and sympathomimetic toxicity associated with recreational use of 1-(3-trifluoromethylphenyl) piperazine (TFMPP) and 1-Benzylpiperazine (BZP). Journal of Medical Toxicology; 4:254-7.

58. Wood DM, Ramsey J, Dargan PI. (2008b); 'Detecting novel and emerging recreational drugs on the 'club scene'. (2008b) Irish Psychiatrist; 9:223-8.

59. Wood DM, Looker J, Shaikh L, Button J, Lidder S, Ramsey J, Holt D, Dargan PI (2009); Seizures associated with recreational use of Bromo-dragonFLY; Journal of Medical Toxicology ;5:226-229

60. Wood DM, Davies S, Puchanarewicz M, Button J, Archer R, Ramsey J, Lee T, Holt DW, Dargan PI. (2010a); Recreational use of 4-methylmethcathinone (4-MMC) presenting with sympathomimetic toxicity and confirmed by toxicological screening. Journal of Medical Toxicology; 6:327-330.

61. Wood DM, Ramsey J, Davies S, Button J, Greene SL. Dargan PI. (2010b); A case series of individuals with analytically confirmed acute mephedrone toxicity. Clinical Toxicology (Philadelphia); 48:924-927.

62. Wood DM, Conran P, Dargan PI. (2011a); ICD-10 coding: poor identification of recreational drug presentations to a large emergency department. Emergency Medical Journal. 28(5):387-9.

63. Wood DM, Greene SL, Dargan PI. (2011b); Clinical pattern of toxicity associated with the novel synthetic cathinone mephedrone. Emergency Medical Journal; 28:280-282.

64. Wood DM, Davies S, Cummins A, Button J, Holt DW, Ramsey J, Dargan PI. (2011c); Energy-1 ('NRG-1'): Don't believe what the newspapers say about it being legal. British Medical Journal; Case Report; DOI:10.1136/bcr.07.2010.3184.

65. Wood DM, Who S, Alldus G, Huggett D, Nicolaou M, Chapman K, Oakley M, Bessim E, Julian K, Sturgeon K, Ramsey JD, Dargan PI. The development of the recreational drug outreach educational concept 'Drug Idle'. Journal of Substance Use 2010;15:237-245.)

66. Woolverton WL, Balster RL. (1983); Effects of local anaesthetics on fixed-interval responding in rhesus monkeys. Pharmacology Biochemistry and Behavior; 18: 383-387.