

ACMD

Advisory Council on the Misuse of Drugs

Consideration of the naphthylpyrovalerone analogues and related compounds.

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

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

7th July 2010

Dear Home Secretary,

The ACMD indicated in its advice of 31st March 2010 on the cathinones that it would provide you with further advice on the naphthyl analogues of pyrovalerone (including naphyrone) and other such analogues. I have pleasure in attaching the Advisory Council on the Misuse of Drugs report on the 'Consideration of the naphthylpyrovalerone analogues and related compounds'.

The ACMD recognise the significant public health issue that 'legal highs' present. Our report references recent work on test purchases of a number of 'legal highs' that demonstrate their many and varied compositions. In this report the evidence highlights the dangers of purchasing compounds which are likely to contain harmful compounds and very often will not be the same as the material advertised and may be more harmful and illegal. Users of 'legal highs' should be acutely aware that just because it is being advertised as legal does not make a substance safe, nor may it be legal.

Along with mephedrone and related compounds, the public health response should focus on the discrepancy between the compounds that are purported to be contained in the 'legal high' for sale and what the customer actually gets. Differences in potency between the apparently identical products could give rise to risk of overdose or unexpected health effects.

As with mephedrone, the ACMD believes that resources should initially be focussed on supply side activities with a concurrent emphasis on educating users. Therefore the ACMD recommends that to curtail the manufacture and supply of naphyrone, and related compounds, an import ban is invoked with immediate effect.

The ACMD believe that naphyrone is likely to exhibit a similar spectrum of harmful effects as the other previously controlled cathinones. The data that are available for naphyrone suggest that its high potency, in comparison with the other cathinones, is likely to be associated with a higher risk of accidental overdose.

The ACMD recommends that naphyrone be brought under control of the Misuse of Drugs Act 1971 in Class B and Schedule I of the Misuse of Drugs Regulations (2003 as amended) by way of a generic definition. Based on the attached evidence, the ACMD consider that the harms associated with naphyrone closely equate with compounds such as mephedrone and other compounds in Class B.

In my letter of 31 March 2010 to your predecessor I indicated that the rapidity with which 'legal highs' have expanded has been exceptional. The ACMD have concerns around this trend and therefore intend to prioritise providing you with advice on 'legal highs', including advice that is wider in scope for protecting the public from the harms of these substances.

Yours sincerely,

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

Professor Les Iversen

Background

- 1.1. In March 2009 the then Home Secretary requested advice from the ACMD on so called 'legal highs'. The ACMD have looked at a number of substances to date and provided advice on GBL, the piperazines (including BZP), the synthetic cannabinoids (including 'Spice) and mephedrone and related compounds.
- 1.1. In a letter to the Home Secretary that accompanied its advice on the cathinones (31 March 2010) the ACMD advised that it would provide further advice on the naphthyl pyrovalerone analogues of cathinone.

2. Introduction

2.1. Naphyrone; (NRG-1; Energy1; or O-2482), naphthylpyrovalerone, is a naphthyl analogue of Pyrovalerone (hereafter referred to as naphyrone) that acts as a triple monoamine reuptake inhibitor, producing psychostimulant effects¹.

2.2. Naphyrone has close structural resemblance to the cathinones such as mephedrone and methylenedioxy-pyrovalerone (MDPV). Naphyrone, however, remains outside the generic definition in which a number of cathinones, including mephedrone and MDPV were controlled under the Misuse of Drugs Act 1971 on 16th April 2010. Since then, websites that had previously offered sales of mephedrone have switched to products purported to be naphyrone and other alternatives. Naphyrone is variously described as:

“The replacement for mephedrone” and “A brand new designer research chemicalfar stronger than cocaine, amphetamine, MDMA”

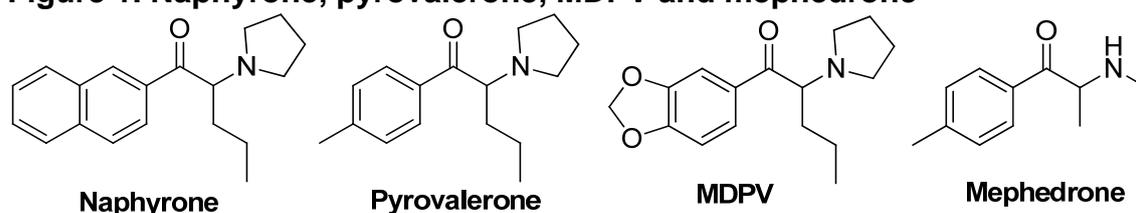
2.3. In this report it is important to distinguish between naphyrone (the subject of the ACMD's advice) and NRG-1; a branded product which may contain naphyrone or any number of other cathinones, legal stimulants (caffeine) or other active and inactive constituents. The branded product NRG-1 cannot be presumed to be naphyrone.

¹ Internationally pyrovalerone is controlled under Schedule IV of the 1971 UN Conventions.

3. Chemical Structure

- 3.1. Naphyrone, is a naphthyl analogue of the cathinones and has close resemblance to pyrovalerone, see Figure 1. Pyrovalerone was used clinically to treat lethargy and fatigue due to its stimulant effects (Gardos and Cole 1971), but its clinical use was largely discontinued due to its association with risks of abuse and addiction (Deniker *et al*, 1975). Pyrovalerone was controlled as a Class C drug under the Misuse of Drugs Act 1971 prior to the inclusion of other cathinones in April 2010.
- 3.2. Meltzer and co-workers (2006) have described the synthesis of naphyrone and a whole range of structurally related pyrovalerone analogues in an attempt to study their ability to release the monoamine neurotransmitters dopamine, serotonin and norepinephrine in the brain.
- 3.3. Naphyrone is more difficult to make than mephedrone and the other legal highs controlled by the cathinone generic classification introduced in April 2010. Its synthesis involves simple reactions, however, the starting materials are not as readily available as the reagents needed for the synthesis of the simpler cathinones such as mephedrone.
- 3.4. The majority of samples purported to contain naphyrone which have been analyzed to date contain other materials such as mephedrone, butylone and other related compounds. However, it is highly possible that the chemists who supply the legal high websites are 'dumping' their old stocks of cathinones (which are now controlled by the generic classification) under the trade name naphyrone (NRG-1). This is fraught with potential problems (see below), particularly if genuine naphyrone becomes more widely available as the dose required is ten-fold less than for mephedrone and this could lead to a significant risk of overdose.

Figure 1. Naphyrone, pyrovalerone, MDPV and mephedrone



4. Pharmacology

- 4.1. There is limited published information on the pharmacology of naphyrone. However, there is considerable pharmacological risk potential in this compound due to its potency, relative to other drugs e.g. mephedrone. Naphyrone has been shown *in vitro* to affect the reuptake of the neurotransmitters dopamine, serotonin and norepinephrine by inhibition of the human monoamine transporters (termed: NET = norepinephrine transporter; SERT = serotonin transporter; and DAT = dopamine transporter).
- 4.2. These transporters are responsible for inactivating the neurotransmitters after their release in the brain, thus making more neurotransmitter available. The drugs may also be taken up by the transporters into nerve endings where they cause a release of the stored neurotransmitter. There are three distinct transporters present in nerves using the three monoamine neurotransmitters.
- 4.3. Naphyrone has considerable abuse potential since it is a triple uptake inhibitor that demonstrates high potency values for inhibition of each of the neurotransmitters². Drugs such as d-amphetamine which interact selectively with the dopamine transporter (DAT) have psychostimulant properties in human users; those such as MDMA (ecstasy) that interact selectively with the serotonin transporter (SERT) have “empathogenic” profiles; while triple uptake inhibitors such as cocaine combine these properties.
- 4.4. Table 1 shows that the potencies of this inhibition are in the low nanomolar (nM) range making naphyrone a potent ‘broad-spectrum’ neurotransmitter releaser which distinguishes this compound from other cathinones. These results predict that naphyrone may have a “cocaine-like” profile, but with approximately ten times higher potency than cocaine. Early reports from human users of naphyrone appear to confirm that the pharmacological dose is indeed very low.

² DA = dopamine, a neurotransmitter involved in the regulation of movement function, energy and drive, appetitive, drug-liking and drug dependence. 5-HT = serotonin, a neurotransmitter involved in many brain functions including regulation of mood and anxiety, eating, sleeping, sexual function and cognition. NE = norepinephrine (noradrenalin), a neurotransmitter involved in the brain and in the peripheral sympathetic nervous system. Drug-induced release of NE in the periphery leads to stimulation of heart and raised blood pressure.

Table 1. Potencies of naphyrone as monoamine uptake inhibitor compared with other drugs of use³

	DA¹ uptake-nM	5-HT uptake-nM	NE uptake -nM
Pyrovalerone	52	>10,000	56
Naphyrone	40	46	12
MDMA (Ecstasy)	1572	238	46
d-Amphetamine	34	3830	39
Cocaine	461	494	378

³ Data from Meltzer et al (2006) and Rothman & Baumann (2003). Values represent the drug concentrations (in nanomolar) required for 50% inhibition of monoamine uptake in test tube model *in vitro*. Lower numbers indicate increased drug potency.

5. Prevalence

- 5.1. The current prevalence of naphyrone use is unknown. However, many of the websites that were previously selling mephedrone now purport to be selling naphyrone through the brand name NRG-1.
- 5.2. Some naphyrone suppliers are marketing the drug for as little as 25p a dose (£12.50 / gram) (or 1kg for £2,500). Some internet based retailers are selling naphyrone (NRG-1) as a premium based plant food or pond cleaner.
- 5.3. The government acted on ACMD advice to control mephedrone and other substituted cathinones, under the Misuse of Drugs Act 1971, on the 29th March 2010 - these became controlled drugs on 16th April 2010. It is a concern that Google trends data on NRG-1 searches indicates a spike in searches in the latter half of April 2010.

Test Purchasing

- 5.4. A publication by Davies *et al* (2010), references test purchases made from the 'legal highs' market before the 2010 legislation concerning the cathinones. The paper does not reference NRG-1 as a branded product.
- 5.5. However, a publication by Brandt *et al* (2010) from Liverpool John Moores University showed analyses of test purchases in April-May 2010. The 'legal highs' purchased were marketed as NRG-1, NRG-2 and MDAI (purchasers probably assuming these to be and/or product descriptions being; naphyrone, dimethocaine and 5,6-methylenedioxy-2-aminoindane respectively). Of seventeen products purchased from 12 UK-based websites following the ban on mephedrone and related compounds, composition varied dramatically and represented a range of controlled compounds and did not, in the main, reflect the product description.
- 5.6. Test purchasing, of a relatively small number of samples, conducted by Tic Tac Communications has shown that naphyrone is often mislabeled, and the substance sold is often a combination of MDPV and/or butylone (results to be published). However, genuine samples of naphyrone have also been detected.
- 5.7. The mislabeling of products may reflect a temporary shortage of supply, or a desire to offload cathinones and other compounds that could previously have been sold legally.
- 5.8. The Association of Chief Police Officers in Scotland (ACPOS) announced that NRG-1 is becoming extensively available throughout Scotland, with the drug advertised as a legal product through UK websites and 'expert' stores. However, tested samples have been shown to contain methylenedioxy-pyrovalerone (MDPV) – a substance brought into Class B of the Misuse of Drugs Act 1971 in April 2010.

5.9. Limited samples of test purchasing would suggest that the prevalence of the compound naphyrone is currently relatively low and makes up a relatively small percentage of the total compounds found in marketed 'legal highs'.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)

5.10. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has announced that they have received a 'Reporting Form' from the Swedish National Focal Point, notifying two seizures of powder of 10g and 288g of naphyrone respectively.

5.11. The EMCDDA has opened a new profile for naphyrone⁴ and has requested analytical details to facilitate its identification.

⁴ The EMCDDA gives drug profiles containing descriptions of drugs in the form of public access 'drug profiles' located at: <http://www.emcdda.europa.eu/publications/drug-profiles>. The profiles are presented in a standardised way, each profile briefly gives the chemistry, pharmacology, synthesis and precursors of each substance, as well as analysis, physical form (e.g. powder, tablet) and mode of use (e.g. ingested, snorted, injected).

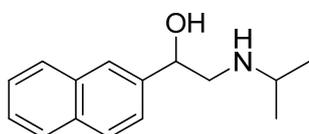
6. Physical harms

Routes of administration

- 6.1. Naphyrone is usually sold as a white crystalline powder.
- 6.2. As with other so-called 'legal highs', users of NRG-1 (believing it to contain naphyrone) may insufflate or swallow the substance, either by dabbing a moistened finger into the product or wrapping in a cigarette paper and 'bombing'. Given the very small quantities required for an active dose of naphyrone, these methods of administration provide an unreliable measure of dosage.

Adverse Effects

- 6.3. Currently very little safety or toxicity data are available for naphyrone, but its high potency by comparison with previous cathinones or MDMA (ecstasy) suggests that its use is likely to be associated with a higher risk of accidental overdose. It is apparent that some suppliers are aware of this and recommend a dose as small as 0.02g, by comparison with the 5-10 times higher doses associated with MDMA or mephedrone.
- 6.4. Consistent with the known or reported harms of the cathinones and traditional amphetamines the predicted harmful effects of naphyrone include adverse effects on the heart and blood vessels, hyperthermia, dependence liability, and psychiatric effects including psychosis and anxiety. In extreme cases amphetamine-like drugs can cause death due to cardiovascular collapse or heat shock (ACMD Report on Cathinones, March 2010).
- 6.5. Another long term concern is that substances containing naphthyl substituents are generally avoided in medicinal chemistry, owing to their potential risk as carcinogens, possibly after metabolism of the naphthyl ring to a highly reactive naphthalene epoxide (Clayson *et al*, 1958). The clinical development of the beta-blocker prothanolol, for example, which bears some close structural resemblance to naphyrone, was abandoned because of its carcinogenicity in animal tests (Howe, 1965; Stapleton, 2007).



Prothanolol

Accident and Emergency Presentations

- 6.6. Guy's and St Thomas' Hospital have seen individuals presenting with acute recreational drug toxicity where use of NRG-1 was reported. However, toxicological analysis of biological samples from these individuals did not detect naphyrone, but instead detected a combination of other cathinones. Therefore, there have been no confirmed cases of

acute toxicity associated with the use of naphyrone. It is therefore apparent that NRG-1 may not often contain controlled substances, such as other cathinones, rather than naphyrone.

- 6.7. Two further cases of potential NRG-1 use have been reported by the North Wales Police, following which two individuals were taken to Wrexham Meallier Hospital. It remains unclear whether the substance the individuals took was naphyrone.

7. Societal harms

Anti-social behaviour / acquisitive crime

7.1. The ACMD is not aware of any relationship between naphyrone and anti-social behaviour or acquisitive crime.

Organised crime

7.2. It would appear that, at present, the retail trade in NRG-1 (purported to be naphyrone) and other emergent so-called legal highs operates mainly through importation and distribution via internet websites; many of which were previously marketing mephedrone and other substituted cathinones controlled in the UK in April 2010.

8. Conclusions

Public Health

- 8.1. The ACMD consider that the public health response to naphyrone, related compounds and other legal highs is a pressing issue.
- 8.2. The control of mephedrone and other cathinones under the Misuse of Drugs Act 1971 appears to have precipitated a shift in the products now offered for sale on the internet. This includes products marketed as naphyrone (NRG-1), but also a range of other compounds e.g. NRG-2 and MDAI (purported to be 5,6-methylenedioxy-2-aminoindane). Subsequent test purchase and analysis of these 'new' so-called 'legal highs' shows that the composition of these products varies and is rarely the purported product for sale (Brandt *et al*, 2010). From the limited samples analysed, from test purchasing, it appears that the market has changed the branding of products rather than changed the products themselves.
- 8.3. The ACMD have identified two concerns about this development. Firstly, the users of 'legal highs' may be at least partially motivated by a desire to buy a legal psychoactive substance rather than an illegal one. However, test purchasing would suggest that in fact there is a considerable risk that they are inadvertently purchasing an illegal substance. Secondly, and of considerable concern as mentioned above, is the potential for overdose: users who purchase a named product, when purchasing that product for a subsequent time, may receive a product of different composition to their first purchase. Differences in potency between the apparently identical branded products could give rise to risk of overdose or unexpected pharmacological effects. This is particularly significant in the case of NRG-1: whilst analyses suggest that NRG-1 is currently likely to contain varying mixtures of controlled substituted cathinones, if this changes to naphyrone (of much higher potency than substituted cathinones), the risk of overdose is much higher.
- 8.4. The potency of naphyrone is such that users only require a dose of approximately 25mg to have an effect. Since this dose is a very small amount it is unlikely that users will be able to, with any accuracy, measure out this amount.
- 8.5. Given the significant legal and health risks to users outlined in 8.3 and 8.4, a concerted public health and education campaign is required which highlights the inconsistencies in the content of these products, the variable potency, risk of overdose and the possibility that users are purchasing drugs which are already controlled under the Misuse of Drugs Act 1971.

Importation, control (under the Misuse of Drugs Act 1971) and regulation

- 8.6. The ACMD considered four options that are presented in Annex 1.

- 8.7. The ACMD consider that the harms associated with naphyrone and related compounds are commensurate with those of mephedrone and therefore those substances in Class B; therefore the ACMD recommend that naphyrone and its close structural analogues be controlled as Class B substances under the Misuse of Drugs Act 1971.
- 8.8. The ACMD recommend that naphyrone and related compounds should be controlled by a generic definition under the Misuse of Drugs Act 1971 – see Annex 1 (option 4), and in schedule 1 of the Misuse of Drugs Regulations 2001 (as amended).
- 8.9. Furthermore, the ACMD recommend that, with immediate effect, the government introduce an import ban by amending the Open General Import Licence (OGIL) to exclude naphyrone from its scope; thereby creating a ban under the Import of Goods Control Order 1954.

Reference compounds and analysis

- 8.10. There is an urgent need for a national chemistry resource capable of providing such reference samples as novel psychoactive substances emerge. The ACMD note that the lack of availability of certified standards of naphyrone could create a problem with the forensic analysis of potential naphyrone samples; this may be met by a recommendation to Research Councils to initiate research calls in this area.
- 8.11. The present availability and manufacture of reference compounds and analytical capability may hamper forensic testing and any subsequent enforcement response to legislative changes.
- 8.12. The ACMD further note the need for research on emergent trends in drug use, their consequences and the implications for drug policy, which should be seen as a priority for the social research community and social science research bodies.

Uses

- 8.13. The ACMD are unaware of any medical or industrial uses of the compounds covered by the generic scope advised.

9. Recommendations

The ACMD make the following recommendations:

- 9.1. A public health and education campaign which warns of the harms likely to be associated with naphyrone. The campaign should also highlight the inconsistencies in the content of these products, the variable potency, risk of overdose and the possibility that users are purchasing drugs which are already controlled under the Misuse of Drugs Act 1971.
- 9.2. Naphyrone and related compounds should be controlled as Class B substances by a generic definition under the Misuse of Drugs Act 1971, and in schedule 1 of the Misuse of Drugs Regulations 2001 (as amended).
- 9.3. The government introduce an import ban on naphyrone with immediate effect.
- 9.4. The resource capability for providing reference samples, as novel psychoactive substances emerge, should be strengthened.
- 9.5. Research on emergent trends in drug use ('legal highs'), their consequences and the implications for drug policy, should be seen as a priority for the social research community and social science research bodies.

10. References

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Annex 1. Options considered by the ACMD

Option 1

Encourage greater reporting and evidence gathering and provide further advice to ministers as information becomes available.

Option 2

Classify as a stand alone substance; so that naphthylpyrovalerone (NRG-1) is controlled under the Misuse of Drugs Act 1971. This would bring naphthylpyrovalerone into line with other cathinones therefore closing the loop-hole that currently exists.

Option 3

Invoke the open general licence to ban the import of naphthylpyrovalerone – this would be in conjunction with options 1, 2 or 4.

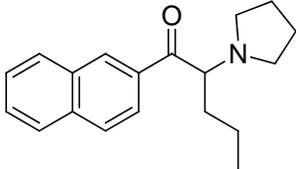
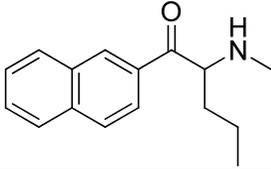
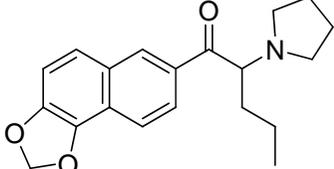
Option 4

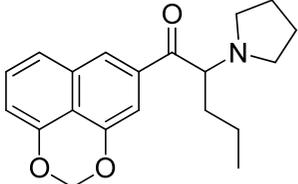
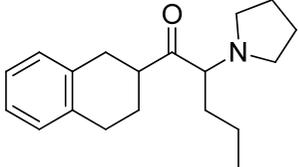
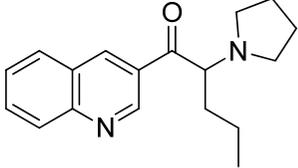
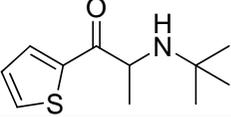
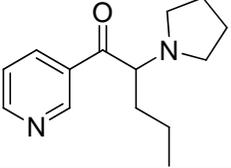
Extend the generic definition of the cathinones to include naphthylpyrovalerone (NRG-1) therefore allowing naphyrone to be controlled under the Misuse of Drugs Act 1971. The recommended definition is:

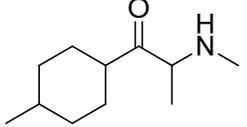
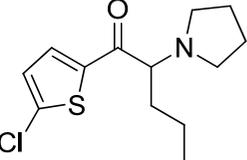
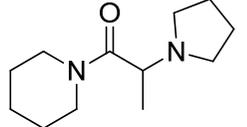
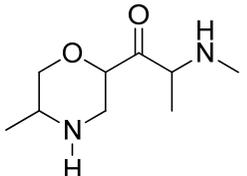
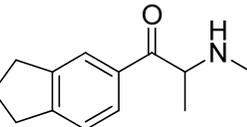
“Any compound structurally derived from 2-aminopropan-1-one by substitution at the 1-position with any monocyclic, or fused-polycyclic ring system (not being a phenyl ring or alkylendioxyphenyl ring system), whether or not the compound is further modified in any of the following ways, that is to say,

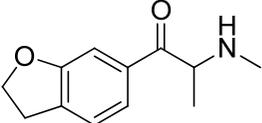
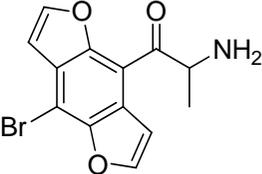
- (i) by substitution in the ring system to any extent with alkyl, alkoxy, haloalkyl or halide substituents, whether or not further substituted in the ring system by one or more other univalent substituents;*
- (ii) by substitution at the 3-position with an alkyl substituent;*
- (iii) by substitution at the 2-amino nitrogen atom with alkyl or dialkyl groups, or by inclusion of the 2-amino nitrogen atom in a cyclic structure.”*

Annex 2. Drugs controlled under the proposed generic definition (the list is not exhaustive)

Name and Structure	DAT (Ki)	SERT (Ki)	NET (Ki)	Ref	Within Scope
Naphyrone, O-2482, NRG-1, [Naphthylene analogue of pyrovalerone] 	20.1	199	37.8	Meltzer <i>et al.</i> , 2006	Yes
[naphth-1-yl isomer of naphyrone] 	?	?	?	?	Yes
<i>N</i> -Methyl analogue of naphyrone 	?	?	?	?	Yes
Methylenedioxy analogue of naphyrone 	?	?	?	?	Yes [fused polycyclic ring system]

Name and Structure	DAT (Ki)	SERT (Ki)	NET (Ki)	Ref	Within Scope
Methyleneedioxy analogue of naphyrone 	?	?	?	?	Yes [fused polycyclic ring system]
[Tetralin analogue of naphyrone] 	?	?	?	?	Yes
Quinoline analogue of naphyrone 	?	?	?	?	Yes
[Compound 3] 	>10uM	>10uM	>10uM	Lancelot <i>et al.</i> , 1992	Yes
Pyridine analogue of pyrovalerone 	?	?	?	?	Yes

Name and Structure	DAT (Ki)	SERT (Ki)	NET (Ki)	Ref	Within Scope
Cyclohexane analogue of mephedrone 	?	?	?	?	Yes
[Compound 17] 	70	?	?	Carroll <i>et al.</i> , 2009	Yes
	?	?	?	?	Yes
Morpholino analogue of mephedrone 	?	?	?	?	Yes
Alkylene derivative of mephedrone 	?	?	?	?	Yes

Name and Structure	DAT (Ki)	SERT (Ki)	NET (Ki)	Ref	Within Scope
Alkyleneoxy derivative of mephedrone 	?	?	?	?	Yes
Bromo-DragonFLY analogue 	?	?	?	?	Yes

Annex 3. Members of the Advisory Council on the Misuse of Drugs

Member	Sector
Professor Leslie Iversen (ACMD Chair)	Professor of Pharmacology, Oxford University
Dr Dima Abdulrahim	Briefings Manager, National Treatment Association
Lord Victor Adebawale	Chief Executive, Turning Point
Dr Jason Aldiss	Veterinary Medicine and Public Health - Managing Director of Eville & Jones Ltd
Mrs Gillian Arr-Jones	Chief Pharmacist for the Care Quality Commission
Mr Martin Barnes	Chief Executive, Drugscope
Dr Margaret Birtwistle	Specialist General Practitioner, Senior Tutor – Education and Training Unit, St George's Hospital and Forensic Medical Examiner
Commander Simon Bray	Commander, Metropolitan Police
Dr Roger Brimblecombe	Pharmaceutical Industry - pharmacologist
Ms Carmel Clancy	Principal Lecturer for Mental Health and Addiction, Middlesex University
Professor Ilana Crome	Professor of Addiction Psychiatry, Keele University
Ms Robyn Doran	Mental Health Nurse and Director of Operations, North-West London Mental Health Trust
Professor Simon Gibbons	Professor of Phytochemistry (natural product chemistry), School of Pharmacy, University of London
Mr Patrick Hargreaves	Advisor for Drugs and Alcohol, Durham County Council Education Department
Ms Caroline Healy	Children's Strategic Adviser
Professor Raymond Hill	Professor of Pharmacology, Imperial College London

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