ACMD

Advisory Council on the Misuse of Drugs

Consideration of the major cannabinoid agonists

ACMD

Advisory Council on the Misuse of Drugs

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Rt Hon Alan Johnson MP
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16th July 2009

Dear Home Secretary,

I outlined in my letter of 8th April 2009 that I would write to your predecessor with advice regarding the synthetic cannabinoid receptor agonists (hereafter termed 'synthetic cannabinoids') which includes the smoking mixture 'Spice'. The ACMD has now considered the issue further and I am pleased to present to you our advice in the attached report.

Forensic analysis of herbal material purported to have psychotropic effects recently revealed the presence of synthetic cannabinoids. It would appear that these synthetic compounds had been sprayed onto a plant based mix (that does not contain tobacco or cannabis) for the purposes of achieving intoxication from smoking. Samples analysed in UK, German and other laboratories have been found to contain synthetic cannabinoids that are believed to be of a higher potency than tetrahydrocannabinol (THC): the active principle in cannabis. We have received reports that such mixes are commonly available for purchase over the internet and also in 'head-shops'. The ACMD has been made aware of the brand 'Spice' under which some material is marketed.

Our report explains that the detailed pharmacology of these synthetic compounds is, as yet, unknown. There are also a large number of potential cannabinoids that could be synthesised. However, some inferences can be made based on the chemistry of the drugs identified to date and it is very likely that these synthetic cannabinoids will produce harmful effects similar to those associated with THC. Indeed, our report notes that the substances containing the synthetic cannabinoids have the potential to be more harmful than cannabis due to their method of manufacture and that the compounds present and their quantity (and hence potency) is unknown to the user.

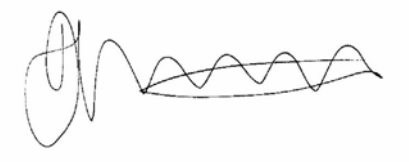
After consideration of the available evidence, the ACMD concludes that with respect to the classification of substances under the Misuse of Drugs Act, the harms of the synthetic cannabinoids are broadly commensurate with those of cannabis and that they should be classified accordingly.

The ACMD also recommends that, with named exemptions, the synthetic cannabinoids are placed in Schedule 1 of the Misuse of Drugs Regulations (1975 – and as subsequently amended) on the grounds they have no recognised medicinal use. We recommend that nabilone, as a component of an existing medicinal product (Cesamet) should be placed in Schedule 2 of the Misuse of Drugs Regulations (2001).

The report also notes that the ACMD has carefully considered advising generic legislation to control these substances under the Misuse of Drugs Act 1971. Presently, only a small number of synthetic cannabinoids have been identified in 'Spice'. However, the potential range of substances presents some challenges to ensure that any legislative changes are not easily subverted by manufacturers changing the compounds they add to the plant-based mix. This concern is supported by recent experience in Germany that suggests that should one of the cannabinoids be controlled, manufacturers move to adding a chemically different, yet functionally similar, synthetic cannabinoid in the 'Spice' mix. Due to the number of variations, it is highly likely that specific legislation would always run some way behind the availability of a legal mix on the street. The ACMD therefore proposes generic legislation to control the synthetic cannabinoids that are, or could in the future, be used in preparations, without impacting on any legitimate use of these or related substances. Five substances are proposed for control by name.

I would welcome the opportunity to meet with you should you want to discuss these matters.

Yours faithfully,



Professor David Nutt FMed Sci

1. Background

In March 2009 the former Home Secretary requested advice on legal highs and 'Spice' in particular. The ACMD wrote to the Home Secretary (Annex B) setting out the ACMD's current thinking on Spice. The ACMD considered the synthetic cannabinoids at a Technical meeting (10th March 2009) and at Council meetings on the 24th March 2009 and 14th May 2009.

This report draws on much of the evidence cited in the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) recent assessment[1] of synthetic cannabinoids, based on an expert meeting held in Lisbon on 6th March 2009.

[1] http://www.emcdda.europa.eu/drug-situation/new-drugs

2. Introduction

For the purposes of this report we term the synthetic cannabinoid agonists as 'synthetic cannabinoids'. In the strictest chemical-structure sense many of the substances named in this report are not cannabinoids, nevertheless the term is widely used to refer to these chemically unrelated structures as they are cannabinoid-like in their activity.

The synthetic cannabinoids considered in this report are CB_1 receptor agonists. The CB_1 receptor in the brain mediates the psychoactive effects of tetrahydrocannabinol (THC), the active principle in cannabis. The synthetic cannabinoids thus mimic the effects of THC. Developed by the pharmaceutical industry and academic laboratories over the past 40 years, they were investigated as potential pharmaceutical agents, often for the treatment of pain, but it proved impossible to separate the desired activity from unwanted psychoactive effects.

Forensic analysis of a number of herbal materials recently revealed the presence of synthetic cannabinoids. It would appear that these synthetic compounds had been sprayed onto a plant-based mix (that does not contain tobacco or cannabis) for the purposes of achieving intoxication from smoking. The plant-based mixes are commonly available over the internet and also in 'head-shops'.

'Spice' is an example of a brand name for a mixture of herbs that are sold in 'head shops' in Europe, Canada and New Zealand as an incense or room odouriser, as well as through Internet sites as an herbal smoking blend. The substance is usually smoked in the belief that it will deliver 'cannabis-like effects'. The drug is also known as 'Spice Silver', 'Spice Gold', 'Spice Diamond', 'Spice Arctic Synergy' and 'Spice Yukatan Fire'. Spice Gold can be brought for £20 (3g) through Internet sites.

Herbs that are listed on the packaging include; *Canavalia maritima*, *Nymphaea caerulea, Scutellaria nana, Pedicularis densiflora, Leonotis leonurus, Zornia latifolia, Nelumbo nucifera* and *Leonurus sibiricus.* However, following analyses by German Laboratories it was found that many of the listed ingredients were not present. Instead, large amounts of synthetic tocopherol (Vitamin E) were present, possibly intended to mask the analytical detection of the active cannabinoids.

3. Structural classification

The synthetic cannabinoid receptor agonists fall into seven major groups[2]:
(1) naphthoylindoles;
(2) naphthylmethylindoles;
(3) naphthoylpyrroles;
(4) naphthylmethylindenes;
(5) phenylacetylindoles (i.e. benzoylindoles);
(6) cyclohexylphenols;
(7) classical cannabinoids (dibenzopyrans);

[2] See tables 1-7, Annex A

Compounds in Groups (1-5) were largely synthesised by Huffman *et al*., (JWH compounds) at Clemson University, USA, during the past 15 years. The cyclohexylphenols (CP compounds) were developed by Pfizer during the 1970's and 1980's, whereas the synthesis of the classical cannabinoids began in the 1960's following the elucidation of the chemical structure of THC.

The only cannabinoids to be licensed as medicines in the UK, albeit with restricted use, are THC (dronabinol) and nabilone; their structures are included in table 7 below for comparison. Although other miscellaneous synthetic cannabinoids are known (see e.g. Refs 4 and 9), they are either weak agonists at the CB_1 receptor or are receptor antagonists or mixed agonists/antagonists, hence they have little if any psychotropic actions and so are not considered here. A further complication with some cannabinoids is that they may show physiological effects unrelated to cannabinoid receptors.

The tables (1-7) in Annex A show the structural skeleton of each group, the substitution pattern and mean affinity constants (K_i) for the CB_1 receptor. High affinity is defined here as K_i < 100nM. It is unlikely that low-affinity agonists (K_i > 100nM) would prove attractive to illicit users. For example, THC (K_i = 10.2nM) is approximately ten times more potent than a substance with K_i = 100nM.

There are a number of gaps in the numerical sequence of the JWH compounds, but many of the 'missing' structures are selective agonists or antagonists of the CB_2 cannabinoid receptor and have limited potential for misuse.

4. Prevalence

The EMCDDA has conducted a short survey of European Union Member States to collect basic information on the availability of products containing synthetic cannabinoids. The questionnaire that was sent contained questions on 'Spice' products and JWH-018, but did not include other specific compounds (e.g. CP 47,497) as these have only subsequently been reported. The returns found that 'Spice' products were identified in 21 of the 30 participating countries (EMCDDA, 2009). In this survey 'identification' was defined as available – not necessarily requiring forensic analysis. However, Spice products and/or JWH-018 have been positively identified by toxicological or forensic analysis in 8 out of those 21 countries where such products were available.

However, data on prevalence are limited as in most member states, as in the UK, these substances are not controlled and are therefore unlikely to be submitted for forensic analysis. Because they represent a very recent phenomenon, there have been no published population, household or user surveys.

Recent forensic analysis (June 2009) of test purchased UK samples from UK websites of 'Spice-like' products has shown the presence of JWH-018, CP 47,497 and HU-210[3].

To a large extent, 'Spice' and related products are sold via Internet sites located in the UK and many other countries. Sales are also made via 'head shops'. The size of this market is unknown but we are aware it is extensive and the networks of distribution are well developed.

5. Physical and Social harms

Evidence concerning the harms of these synthetic cannabinoids is not well understood nor well published because of their recent appearance on the market. However the EMCDDA recently published a briefing paper that sets out the key issues and identifies potential harms[4].

The EMCDDA note in their report (2009) that a number of *in vitro* and animal studies have been published (including derivation of structure activity relationships). However, there are no pharmaceutical products that have emerged nor are there human studies on these compounds (EMCDDA, 2009).

Physical and mental harms

The specific risks users take with the synthetic cannabinoids are, in part, unknown as neither their metabolism nor their toxicology has been extensively studied. Considering the harms of the synthetic cannabinoids analogous to those of THC may underestimate their potential harms.

Because substances that contain the synthetic cannabinoids are manufactured, there can be considerable inter-and intra-batch variability, both in terms of substances present and quantity. Users cannot therefore assume the same effects from the same product the next time they use it. Thus, there is potential for overdose should a person use a particularly strong batch or a synthetic cannabinoid with particularly high potency. What the clinical outcomes of such an overdose would be can, at present, only be speculated, but are likely to include significant alterations in mental state with paranoia and perceptual disruptions such as are produced by high THC exposure.

Pigee (2009) refers to media reports from Germany where a number of users of 'herbal incense' presented to emergency rooms with psychosis-like panic attacks and heart and circulatory problems (also see Auwarter, 2009).

The EMCDDA report (2009) suggests that tolerance to these synthetic cannabinoids may develop fairly fast. There are therefore concerns that users may be at a greater risk of developing dependence. Evidence of a withdrawal effect after smoking 'Spice Gold' has been reported by Zimmermann *et al*. (2009).

[3] http://www.ltg.uk.net/admin/files/Spice.pdf
[4] http://www.emcdda.europa.eu/drug-situation/new-drugs

Societal harms
As there are no estimates of the number of users of Spice, either in the UK or other EU countries it is difficult to estimate the current societal harms. However, it is plausible to expect that the societal harms have the *potential* to be comparable to those of cannabis.

6. Options for control

Specific control of substances offers the simplest approach, but not only would this require the listing of a large number of compounds by their systematic names, there is a risk that any such list would not be exhaustive. In other words, non-controlled (designer) analogues could rapidly appear on the illicit market.

Generic control is appropriate for groups of substances where:

- Relatively simple substitution patterns occur in a structural nucleus
- A large number of examples are already known
- Synthesis of further analogues might be anticipated
- The target group can be encompassed with a simple definition.

6.1. ***Generic control***

The following generic definitions for the major groups of cannabinoids are proposed. For Groups 1- 6, N refers to the number of examples shown in the tables in Annex A.

Table 1 and 2: Groups 1 and 2 (Naphthoylindoles and naphthylmethylindoles)
(N = 74 and 9 respectively)

"Any compound structurally derived from 3-(1-naphthoyl)indole or 1*H*-indol-3-yl-(1-naphthyl)methane by substitution at the nitrogen atom of the indole ring by alkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl or 2-(4-morpholinyl)ethyl whether or not further substituted in the indole ring to any extent , whether or not substituted in the naphthyl ring to any extent."

Table 3: Group 3 (Naphthoylpyrroles)
(N = 32)

"Any compound structurally derived from 3-(1-naphthoyl)pyrrole by substitution at the nitrogen atom of the pyrrole ring by alkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl or 2-(4-morpholinyl)ethyl, whether or not further substituted in the pyrrole ring to any extent ,whether or not substituted in the naphthyl ring to any extent.."

Table 4: Group 4 (Naphthylmethylindenes)
(N = 3)

"Any compound structurally derived from 1-(1-naphthylmethyl)indene by substitution at the 3-position of the indene ring by alkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl or 2-(4-morpholinyl)ethyl whether or not

further substituted in the indene ring to any extent, whether or not substituted in the naphthyl ring to any extent."

Table 5: Group 5 (Phenylacetylindoles)
(N = 28)

"Any compound structurally derived from 3-phenylacetylindole by substitution at the nitrogen atom of the indole ring with alkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl or 2-(4-morpholinyl)ethyl, whether or not further substituted in the indole ring to any extent, whether or not substituted in the phenyl ring to any extent."

Table 6: Group 6 (Cyclohexylphenols)
(N = 16)

"Any compound structurally derived from 2-(3-hydroxycyclohexyl)phenol by substitution at the 5-position of the phenolic ring by alkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl or 2-(4-morpholinyl)ethyl, whether or not substituted in the cyclohexyl ring to any extent ."

6.2. ***Specific control***
In Part IV of Schedule 2 of the Misuse of Drugs Act, cannabinol derivatives are defined as:

"…the following substances, except where contained in cannabis or cannabis resin, namely tetrahydro derivatives of cannabinol and 3-alkyl homologues of cannabinol or of its tetrahydro derivatives".

This definition captures several cannabinol derivatives as shown in Annex A, table 7 (Group 7), some of which are among the most potent cannabinoids known (Ref 10).

Further substances, as shown below, are commercially available, and are used as research tools. They are potentially misusable, but are not captured by the existing or proposed definitions. In each case, it is suggested that they should be named specifically.

6.2.1
HU-210[5] is a classical cannabinoid closely related to THC. The overarching control of stereoisomers in the Misuse of Drugs Act would normally apply automatically to all of the cannabinoid groups considered here if they became controlled drugs. However, the 6*aR*,10*aR* enantiomer of HU210 (known as HU-211 or dexanabinol; Ref 4) is a non-psychotropic cannabinoid with antagonist actions at the NMDA glutamate receptor. It has some potential as a neuroprotective agent and could be made exempt, as required, by license.

[5] 9-(Hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,10,10a-tetrahydrob enzo[c]chromen-1-ol

6.2.2.
Nabilone[6] is also chemically related to THC. It is a component of an existing medicinal product (Cesamet), but is not widely used.

6.2.3
WIN-55,212-2[7] is closely related to the naphthoylindoles in Group 1.

6.2.4
HU-243[8] is chemically related to THC.

6.2.5
CP 50,5561[9], one stereoisomer of which is known as levonantradol, is closely related to the substances shown in Group 6.

6.2.6
[*This paragraph has been withheld on the ground that its publication would not be in the public interest.]*

7.
[*This paragraph has been withheld on the ground that its publication would not be in the public interest.]*

[6] 1-Hydroxy-6,6-dimethyl-3-(2-methyloctan-2-yl)-7,8,10,10a-tetrahydro-6*H*-benzo [c]chromen-9(6a*H*)-one
[7] [2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de)-1,4-benzoxazin-6-yl]-1-napthalenylmethanone
[8] 3-dimethylheptyl-11-hydroxyhexahydrocannabinol
[9] 9-hydroxy-6-methyl-3-[5-phenylpentan-2-yl]oxy-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-1-yl]acetate

8. Conclusions/Recommendations

Recommendation 1
The ACMD recommend that the substances detailed in Annex A, herein termed synthetic cannabinoids, have potential harms commensurate with those of cannabis and should be classified and controlled under the Misuse of Drugs Act (1971) accordingly.

Recommendation 2
The ACMD also recommends that, with named exemptions, the above synthetic cannabinoids are placed in Schedule 1 of the Misuse of Drugs Regulations (2001) on the grounds they have no recognised medicinal use. We recommend that nabilone, as a component of an existing medicinal product (Cesamet) should be placed in Schedule 2 of the Misuse of Drugs Regulations (2001).

Recommendation 3
To achieve the required legislation the ACMD recommends that the majority of substances be brought under control by means of generic definitions. However, 5 substances are recommended as being named for specific control: HU-210, nabilone, WIN-55,212-2, HU-243 and CP 50,5561.

Recommendation 4
[*This recommendation has been withheld on the ground that its publication would not be in the public interest.*]

References

Auwärter V, Dresen D, Weinmann W, Müller M, Pütz M and Ferreirós N (2009) Spice and other herbal blends: harmless incense or cannabinoid designer drugs? *Journal of Mass Spectrometry* 44(5): 832 – 837.

EMCDDA (2009) Action on new drugs briefing paper: Understanding the 'Spice' Phenomenon (a report from an EMCDDA expert meeting, 6 March 2009, Lisbon). http://www.emcdda.europa.eu/drug-situation/new-drugs

Pigee C (2009) Investigating a not-so-natural high, *Analytical Chemistry* 81 (9), 3205–3207.

Vann RE *et al*. (2009) Discriminative stimulus properties of Δ^9-tetrahydrocannabinol (THC) in C57BL/6J mice, European Journal of Pharmacology (in press).

Zimmermann US *et al*. Withdrawal phenomena and dependence syndrome after the consumption of "Spice Gold", Dtsch. Arztebl. Int.,106(27), 464-7.

The references below relate to citations in Annex A, tables 1-7.

1. Huffman J W *et al*. (2003) 3-Indolyl-1-naphthylmethanes: new cannabimimetic indoles provide evidence for aromatic stacking interactions with the CB_1 cannabinoid receptor. *Bioorganic and Medicinal Chemistry* 11, 539–549.

2. Available from Cayman chemicals (www.caymanchem.com)

3. Auwärter V, Dresen D, Weinmann W, Müller M,, Pütz M and Ferreirós N (2009) Spice and other herbal blends: harmless incense or cannabinoid designer drugs? *Journal of Mass Spectrometry* 44 (5), 832 – 837.

4. Howlett AC *et al*. (2002) International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacological Reviews* 54(2), 161-202.

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6. Huffman JW *et al*. (2005) Structure–activity relationships for 1-alkyl-3-(1-naphthoyl)indoles at the cannabinoid CB_1 and CB_2 receptors: steric and electronic effects of naphthoyl substituents. New highly selective CB_2 receptor agonists, *Bioorganic and Medicinal Chemistry* 13, 89–112.

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8. Huffman JW (2009) Cannabimimetic indoles, pyrroles, and indenes: structure-activity relationships and receptor interactions. In: *The cannabinoid receptors*, Reggio PH (Ed), Humana Press.

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10. Huffman JW and Duncan SG (1997) Synthesis and pharmacology of the 1',2'-dimethylheptyl-Δ^8-THC isomers; exceptionally potent cannabinoids. *Bioorganic and Medicinal Chemistry Letters*, 7(21), 2799-2804.

11. Compton DR *et al*. (1992) Pharmacological profile of a series of bicyclic cannabinoid analogs: Classification as cannabimimetic agents. *Journal of Pharmacology and Experimental Therapeutics* 260(1), 201-209.

12. Compton DR *et al*. (1993) Cannabinoid structure-activity relationships: Correlation of receptor binding and *in vivo* activities. *Journal of Pharmacology and Experimental Therapeutics*, 265(1), 218.

Annex A.

In the following tables (1-7), the affinity constants (K_i) of the cannabinoid agonists, where known, are listed. The lower the value of K_i, the higher is the expected potency. Although determined in vitro, there is evidence that these constants correlate with pharmacological effects in animals (Vann *et al*., 2009) Furthermore, like the naturally-occurring THC, those synthetic cannabinoids reported in 'Spice' and related products have low K_i values. In the tables, substances with high K_i, values (shown as 'Low affinity for the CB_1 receptor') are unlikely to be misused.

Small discrepancies exist in K_i values for similar substances between different publications. Some structures exhibit geometrical isomerism, where the separate isomers may show different receptor activity, but a distinction is not always made in the published literature. In the following tables, the abbreviation MPE refers to a 2-(4-morpholino)ethyl substituent.

Substances which have been reported in smoking mixtures are shown emboldened/highlighted. The tables also indicate which substances are currently controlled in Germany (D), Austria (A) and France (F).

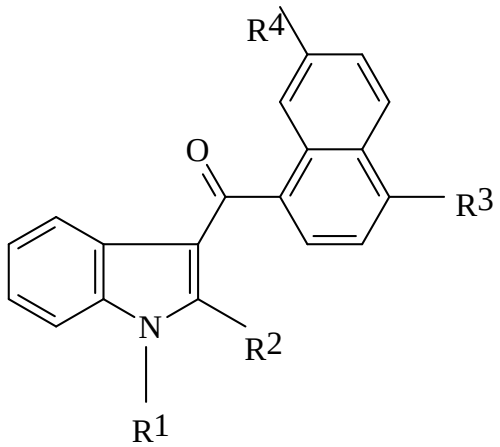

Table 1. Group 1: Naphthoylindoles

Substance	R^1	R^2	R^3	R^4	Comments	K_i (nM)
JWH-004	Hexyl	Methyl	H	H	Ref 8	48
JWH-007	Pentyl	Methyl	H	H	Ref 1	2.9
JWH-009	Heptyl	Methyl	H	H	Ref 8 Low affinity for CB_1 receptor	>1000
JWH-015	Propyl	Methyl	H	H	Ref 2, Ref 6 Low affinity for CB_1 receptor	165
JWH-016	Butyl	Methyl	H	H	Ref 8	22
JWH-018	**Pentyl**	**H**	**H**	**H**	**Ref 1 Controlled in D, A and F.**	**2.9**
JWH-019	Hexyl	H	H	H	Ref 5	9.8
JWH-020	Heptyl	H	H	H	Ref 5 Low affinity for CB_1 receptor	128
JWH-046	Propyl	Methyl	H	Methyl	Ref 6 Low affinity for CB_1 receptor	343
JWH-047	Butyl	Methyl	H	Methyl	Ref 8	59
JWH-048	Pentyl	Methyl	H	Methyl	Ref 6	10.7
JWH-049	Hexyl	Methyl	H	Methyl	Ref 8	55
JWH-050	Heptyl	Methyl	H	Methyl	Ref 8	342
JWH-070	Methyl	H	H	H	Ref 5 Low affinity for CB_1 receptor	>1000
JWH-071	Ethyl	H	H	H	Ref 5 Low affinity for CB_1 receptor	>1000
JWH-072	Propyl	H	H	H	Ref 5 Low affinity for CB_1 receptor	>1000

Group 1: Naphthoylindoles – contd.						
Substance	**R^1**	**R^2**	**R^3**	**R^4**	**Comments**	**K_i (nM)**
JWH-073	**Butyl**	**H**	**H**	H	**Ref 2 (not shown in cited literature)**	**8.9**
JWH-076	Propyl	H	H	Methyl	Ref 6 Low affinity for CB_1 receptor	214
JWH-079	Propyl	H	Methoxy	H	Ref 8	63
JWH-080	Butyl	H	Methoxy	H	Ref 8	7.6
JWH-081	Pentyl	H	Methoxy	H	Ref 1	1.2
JWH-082	Hexyl	H	Methoxy	H	Ref 8	5.3
JWH-094	Propyl	H	Methoxy	H	Ref 8 Low affinity for CB_1 receptor	476
JWH-096	Butyl	H	Methoxy	H	Ref 8	34
JWH-098	Pentyl	Methyl	Methoxy	H	Ref 1	4.5
JWH-116	Pentyl	Ethyl	H	H	Ref 1	52
JWH-120	Propyl	H	Methyl	H	Ref 6 Low affinity for CB_1 receptor	>1000
JWH-122	Pentyl	H	Methyl	H	Ref 1	0.69
JWH-148	Propyl	Methyl	Methyl	H	Ref 6 Low affinity for CB_1 receptor	123
JWH-149	Pentyl	Methyl	Methyl	H	Ref 1	5.0
JWH-180	Propyl	H	Propyl	H	Ref 6	26
JWH-181	Pentyl	Methyl	Propyl	H	Ref 6	1.3
JWH-182	Pentyl	H	Propyl	H	Ref 6	0.65
JWH-189	Propyl	Methyl	Propyl	H	Ref 6	52
JWH-193	MPE	H	Methyl	H	Ref 1	6
JWH-198	MPE	H	Methoxy	H	Ref 1	10
JWH-200	MPE	H	H	H	Ref 1	42
JWH-210	Pentyl	H	Ethyl	H	Ref 6	0.46
JWH-211	Propyl	Methyl	Methyl	H	Ref 6	70
JWH-212	Propyl	H	Ethyl	H	Ref 6	33
JWH-213	Pentyl	Methyl	Ethyl	H	Ref 6	1.5
JWH-234	Pentyl	H	H	Ethyl	Ref 6	8.4
JWH-235	Propyl	H	H	Ethyl	Ref 6 Low affinity for CB_1 receptor	338
JWH-236	Propyl	Methyl	H	Ethyl	Ref 6 Low affinity for CB_1 receptor	>1000
JWH-239	Propyl	H	Butyl	H	Ref 6 Low affinity for CB_1 receptor	342
JWH-240	Pentyl	H	Butyl	H	Ref 6	14
JWH-241	Propyl	Methyl	Butyl	H	Ref 6 Low affinity for CB_1 receptor	147

Group 1: Naphthoylindoles – contd.						
Substance	**R^1**	**R^2**	**R^3**	**R^4**	**Comments**	**K_i (nM)**
JWH-242	Pentyl	Methyl	Butyl	H	Ref 6	42
JWH-262	Pentyl	Methyl	H	Ethyl	Ref 6	28
JWH?	Butyl	H	H	H	Ref 7	8.9
JWH?	Pentyl	H	H	H	Ref 7	9
JWH?	Propyl	Methyl	H	H	Ref 7 Low affinity for CB_1 receptor	164
JWH?	Ethyl	Methyl	H	H	Ref 7 Low affinity for CB_1 receptor	>1000
JWH?	Methyl	Methyl	H	H	Ref 7 Low affinity for CB_1 receptor	>1000
JWH-386	Propyl	H	Br	H	Ref 8 Low affinity for CB_1 receptor	161
JWH-387	Pentyl	H	Br	H	Ref 8	1.2
JWH-394	Pentyl	Methyl	Br	H	Ref 8	2.8
JWH-395	Propyl	Methyl	Br	H	Ref 8 Low affinity for CB_1 receptor	372
JWH-397	Pentyl	Methyl	Cl	H	Ref 8	8.9
JWH-398	Pentyl	H	Cl	H	Ref 8	2.3
JWH-399	Propyl	Methyl	Cl	H	Ref 8 Low affinity for CB_1 receptor	187
JWH-400	Propyl	H	Cl	H	Ref 8	93
JWH-412	Pentyl	H	F	H	Ref 8	7.2
JWH-413	Pentyl	Methyl	F	H	Ref 8	14
JWH-414	Propyl	H	F	H	Ref 8 Low affinity for CB_1 receptor	240
JWH-415	Propyl	Methyl	F	H	Ref 8 Low affinity for CB_1 receptor	530
Not named	2-Pentenyl	Methyl	H	H	Ref 7 Low affinity for CB_1 receptor	340
Not named	4-Pentenyl	Methyl	H	H	Ref 7	38
Not named	Allyl	Methyl	H	H	Ref 7 Low affinity for CB_1 receptor	>1000
Not named	2-Pentenyl	H	H	H	Ref 7	58
Not named	4-Pentenyl	H	H	H	Ref 7	43
Not named	2-Phenylethyl	Methyl	H	H	Ref 7 Low affinity for CB_1 receptor	>1000
Not named	Cyclohexylethyl	Methyl	H	H	Ref 7	46
Not named	Cyclopropylmethyl	Methyl	H	H	Ref 7 Low affinity for CB_1 receptor	140

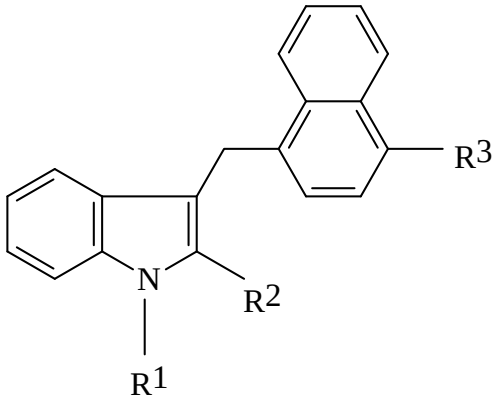

Table 2. Group 2: Naphthylmethylindoles

Substance	R^1	R^2	R^3	Comments	K_i (nM)
JWH-175	Pentyl	H	H	Ref 1	22
JWH-184	Pentyl	H	Methyl	Ref 1	23
JWH-185	Pentyl	H	Methoxy	Ref 1	17
JWH-192	MPE	H	Methyl	Ref 1	41
JWH-194	Pentyl	Methyl	Methyl	Ref 1 Low affinity for CB_1 receptor	127
JWH-195	MPE	H	H	Ref 1 Low affinity for CB_1 receptor	113
JWH-196	Pentyl	Methyl	H	Ref 1 Low affinity for CB_1 receptor	151
JWH-197	Pentyl	Methyl	Methoxy	Ref 1 Low affinity for CB_1 receptor	323
JWH-199	MPE	H	Methoxy	Ref 1	20

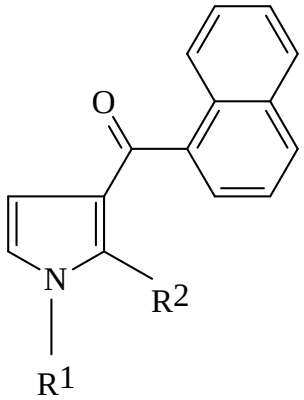

Table 3. Group 3: Naphthoylpyrroles

Substance	R^1	R^2	Comments	K_i (nM)
Unnamed?	Methyl	H	Ref 7 Low affinity for CB_1 receptor	>1000
Unnamed?	Ethyl	H	Ref 7 Low affinity for CB_1 receptor	>1000
Unnamed?	Propyl	H	Ref 7 Low affinity for CB_1 receptor	>1000
Unnamed?	Butyl	H	Ref 7 Low affinity for CB_1 receptor	666
Unnamed?	Hexyl	H	Ref 7 Low affinity for CB_1 receptor	399
Unnamed?	Heptyl	H	Ref 7 Low affinity for CB_1 receptor	309
JWH-030	Pentyl	H	Ref 7	87
JWH-145	Pentyl	Phenyl	Ref 8	14
JWH-146	Heptyl	Phenyl	Ref 8	21
JWH-147	Hexyl	Phenyl	Ref 8	11
JWH-150	Butyl	Phenyl	Ref 8	60
JWH-156	Propyl	Phenyl	Ref 8 Low affinity for CB_1 receptor	404
JWH-243	Pentyl	4-Methoxyphenyl	Ref 8 Low affinity for CB_1 receptor	285
JWH-244	Pentyl	4-Methylphenyl	Ref 8 Low affinity for CB_1 receptor	130
JWH-245	Pentyl	4-Chlorophenyl	Ref 8 Low affinity for CB_1 receptor	276
JWH-246	Pentyl	3-Chlorophenyl	Ref 8	70
JWH-292	Pentyl	2-Methoxyphenyl	Ref 8	29

Group 3: Naphthoylpyrroles - contd.

Substance	R^1	R^2	Comments	K_i (nM)
JWH-293	Pentyl	3-Nitrophenyl	Ref 8 Low affinity for CB_1 receptor	100
JWH-307	Pentyl	2-Fluorophenyl	Ref 8	7.7
JWH-308	Pentyl	4-Fluorophenyl	Ref 8	41
JWH-346	Pentyl	3-Methylphenyl	Ref 8	67
JWH-348	Pentyl	4-Trifluoromethylphenyl	Ref 8 Low affinity for CB_1 receptor	218
JWH-363	Pentyl	3-Trifluoromethylphenyl	Ref 8 Low affinity for CB_1 receptor	245
JWH-364	Pentyl	4-Ethylphenyl	Ref 8	34
JWH-365	Pentyl	2-Ethylphenyl	Ref 8	17
JWH-367	Pentyl	3-Methoxyphenyl	Ref 8	53
JWH-368	Pentyl	3-Fluorophenyl	Ref 8	16
JWH-369	Pentyl	2-Chlorophenyl	Ref 8	7.9
JWH-370	Pentyl	2-Methylphenyl	Ref 8	5.6
JWH-371	Pentyl	4-Butylphenyl	Ref 8	42
JWH-373	Pentyl	2-Butylphenyl	Ref 8	60
JWH-392	Pentyl	2-Trifluoromethylphenyl	Ref 8	77

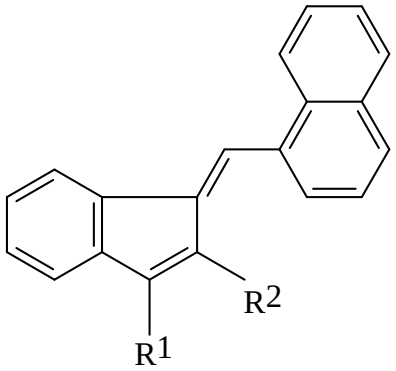

Table 4. Group 4: Naphthylmethylindenes

Substance	R^1	R^2	Comments	K_i (nM)
JWH-176	Pentyl	H	Ref 1	26
Compound #7	MPE	H	Ref 1	2.7
Compound #8	MPE	Methyl	Ref 1	2.9

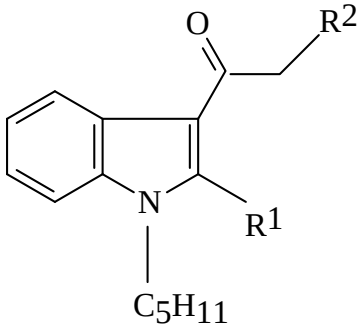

Table 5. Group 5: Phenylacetylindoles

Substance	R^1	R^2	Comments	K_i (nM)
JWH-167	H	Phenyl	Ref 8	64
JWH-201	H	4-Methoxyphenyl	Ref 8 Low affinity for CB_1 receptor	>1000
JWH-202	Methyl	4-Methoxyphenyl	Ref 8 Low affinity for CB_1 receptor	>1000
JWH-203	H	2-Chlorophenyl	Ref 8	8.0
JWH-204	Methyl	2-Chlorophenyl	Ref 8	13
JWH-205	Methyl	Phenyl	Ref 8 Low affinity for CB_1 receptor	124
JWH-206	H	4-Chlorophenyl	Ref 8 Low affinity for CB_1 receptor	389
JWH-207	Methyl	4-Chlorophenyl	Ref 8 Low affinity for CB_1 receptor	>1000
JWH-208	H	4-Methylphenyl	Ref 8 Low affinity for CB_1 receptor	179
JWH-209	Methyl	4-Methylphenyl	Ref 8 Low affinity for CB_1 receptor	746
JWH-237	H	3-Chlorophenyl	Ref 8	38
JWH-248	H	4-Bromophenyl	Ref 8 Low affinity for CB_1 receptor	>1000
JWH-249	H	2-Bromophenyl	Ref 8	8.4
JWH-250	H	2-Methoxyphenyl	Ref 8	11
JWH-251	H	2-Methylphenyl	Ref 8	29

Group 5: Phenylacetylindoles – contd.				
Substance	**R^1**	**R^2**	**Comments**	**K_i (nM)**
JWH-252	Methyl	2-Methylphenyl	Ref 8	23
JWH-253	Methyl	3-Methoxyphenyl	Ref 8	62
JWH-302	H	3-Methoxyphenyl	Ref 8	17
JWH-303	Methyl	3-Chlorophenyl	Ref 8 Low affinity for CB_1 receptor	117
JWH-304	Methyl	4-Bromophenyl	Ref 8 Low affinity for CB_1 receptor	>1000
JWH-305	Methyl	2-Bromophenyl	Ref 8	15
JWH-306	Methyl	2-Methoxyphenyl	Ref 8	25
JWH-311	H	2-Fluorophenyl	Ref 8	23
JWH-312	H	3-Fluorophenyl	Ref 8	72
JWH-313	H	4-Fluorophenyl	Ref 8 Low affinity for CB_1 receptor	422
JWH-314	Methyl	2-Fluorophenyl	Ref 8	39
JWH-315	Methyl	3-Fluorophenyl	Ref 8 Low affinity for CB_1 receptor	430
JWH-316	Methyl	4-Fluorophenyl	Ref 8 Low affinity for CB_1 receptor	>1000

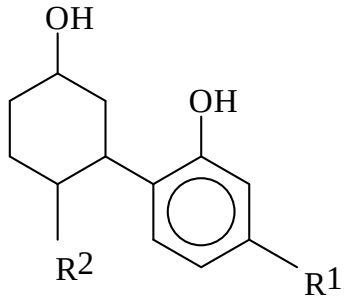

Table 6. Group 6: Cyclohexylphenols

Substance	R^1	R^2	Comments	K_i (nM)
CP-55,940	1,1-Dimethylheptyl	Hydroxypropyl	Ref 1. (aka Analog XIV in Ref 11)	0.35 (Ref 8)
CP-47,497	**1,1-Dimethylheptyl**	**H**	**Ref 3. Controlled in D, A and F (aka Analog VI in Ref 11)**	**9.54**
Analog VII	**1,1-Dimethyloctyl**	**H**	**Ref 3. Controlled in D, A and F (Homologue #1)**	**4.7 (Ref 12)**
Analog V	1,1-Dimethylhexyl	H	Controlled in D, A and F (Homologue #2)	126 (Ref 12)
Analog VIII	1,1-Dimethylnonyl	H	Controlled in D, A and F (Homologue #3)	28.5 (Ref 12)
Analog I	1,1-Dimethylethyl	H	Low affinity for CB_1 receptor	>1000 (Ref 12)
Analog II	1,1-Dimethylpropyl	H	Low affinity for CB_1 receptor	>1000 (Ref 12)
Analog III	1,1-Dimethylbutyl	H	Low affinity for CB_1 receptor	>1000 (Ref 12)
Analog IV	1,1-Dimethylpentyl	H	Low affinity for CB_1 receptor	735 (Ref 12)
Analog IX	1,1-Dimethyldecyl	H	Low affinity for CB_1 receptor	163 (Ref 12)
Analog X	1,1-Dimethylundecyl	H	Low affinity for CB_1 receptor	381 (Ref 12)
Analog XI	1,1-Dimethylheptyl	Methyl	The C_1-α-OH isomer of Analog XII	6.2 (Ref 12)
Analog XII	1,1-Dimethylheptyl	Methyl		7.7 (Ref 12)
Analog XIII	H	Hydroxypropyl	Low affinity for CB_1 receptor	>1000 (Ref 12)
Analog XV	1,1-Dimethylheptyl	Hydroxypropyl	aka CP-56,667	62 (Ref 12)
Analog XVI	1,1-Dimethylheptyl	Hydroxybutyl		1.6 (Ref 12)

Note: Analog numbers follow Table 1 in Ref 11.

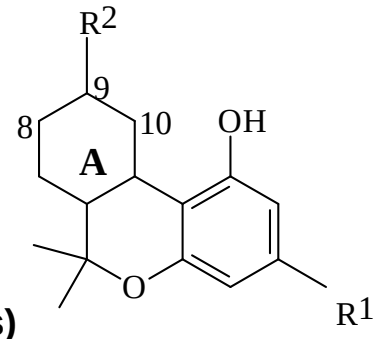

Table 7. Group 7: Classical cannabinoids (Dibenzopyrans)

Substance	R^1	R^2	Comments	K_i (nM)
Δ^9-THC	Pentyl	Methyl	Phytocannabinoid. Unsaturation at C_9-C_{10}. Class B controlled.	10.2 (Ref 8)
Δ^8-THC	Pentyl	Methyl	Phytocannabinoid. Unsaturation at C_8-C_9. Class B controlled.	16.5 (Ref 8)
Nabilone	1,1-Dimethylheptyl	Keto (=O)	Ring A is saturated. Active component of Cesamet®	1.84 (Ref 9)
HU-210	**1,1-Dimethylheptyl**	**Hydroxymethyl**	**Unsaturation at C_8-C_9. Controlled in F.**	**0.06 (Ref 4)**
HU-211	1,1-Dimethylheptyl	Hydroxymethyl	Unsaturation at C_8-C_9. Low affinity for CB_1 receptor	>100? (Ref 4)
unnamed	1,1-Cyclopropylheptyl	Methyl	Unsaturation at C_8-C_9. Class B controlled.	0.44 (Ref 9)
unnamed	1,1-Dimethylcyclohexyl	Methyl	Unsaturation at C_8-C_9. Class B controlled.	? (Ref 9)
unnamed	1,2-Dimethylheptyl	Methyl	Unsaturation at C_8-C_9. Class B controlled.	<1.0 (Ref 10)
unnamed	1,1-Dimethylheptyl	Methyl	Unsaturation at C_8-C_9. Class B controlled.	<1.0 (Ref 10)

Note: HU-211 is the 6*aS*,10*aS* enantiomer of HU-210, which is itself 6*aR*,10*aR* (Ref 4).

Annex B. Letter to Home Secretary re: ACMD concerns

ACMD

Advisory Council on the Misuse of Drugs

Chair: Professor David Nutt
Secretary: Will Reynolds

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

Rt Hon Jacqui Smith
2 Marsham Street
London
SW1P 4DF

8th April 2009

Dear Home Secretary,

I outlined in my letter of 31st March 2009 that I would write to you with initial advice regarding the drug 'Spice'. The ACMD has received presentations on 'Spice' from a member associated with the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and has discussed the subject at some length at its recent technical committee meeting.

Such is the concern regarding 'Spice' in the ACMD that I consider it timely to raise the issue with you now, while the Council is still developing its formal advice to you, which I hope to have completed by the end of May.

'Spice' is a plant based smoking mix that does not contain tobacco. It is marketed as a herbal product almost exclusively on the internet. Products analysed in German samples have been found to contain synthetic cannabinoids that are believed to be of a higher potency than tetrahydrocannabinol (THC): the active principle in cannabis. Their detailed pharmacology is, as yet, unknown due, in part, to the large number of potential cannabinoids that can be synthesised. However, the ACMD's chemists and pharmacologists can make some inferences based on the chemistry of the drugs identified to date and it is very likely that these synthetic cannabinoids will produce all the harmful effects that are associated with THC.

The MHRA has written to three UK suppliers (October 2008) informing them that 'Spice Gold' is a medicinal product. All three companies have decided to cease sale and supply. However, we believe that this action has had little no effect on the supply of "Spice" in the UK either through internet or retail sales.

Currently, Austria, Germany and France in the EU have controlled those synthetic cannabinoids identified in Spice and an approximately similar number of other Member States have legislation pending.

Presently, only a small number of synthetic cannabinoids have been identified in ‘Spice’. However, the potential range presents some challenges to ensure that any legislative changes are not easily subverted by manufacturers (which appear mainly to be based in China) changing the compounds they add. This concern is supported by recent experience in Germany that suggests that should one of the cannabinoids be controlled, manufacturers move to adding a chemically different, yet functionally similar, synthetic cannabinoid in the ‘Spice’ mix. Due to the number of variations, it is highly likely that specific legislation would always run some way behind the availability of a legal mix on the street. Therefore, the ACMD is considering how best to use generic legislation to control the cannabinoids that are, or could in the future, be used in ‘Spice’, without impacting on any legitimate use of these or related substances.

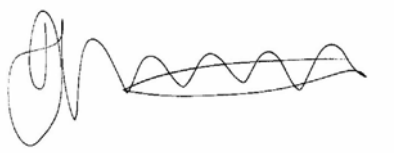
Although the synthetic cannabinoids fall within the definition of ‘new psychoactive substances’ as defined by EU Council Decision 2005/387/JHA, it is considered unlikely that the EMCDDA and Europol could carry out a risk assessment on more than a few representative members of the group.

We aim to provide you with advice on classification, potential generic legislation and other recommendations in the minimum time necessary to complete our considerations. I have requested the ACMD Secretariat to regularly update your policy officials so that you are kept informed of our progress on this important matter.

The example of ‘Spice’ has prompted the ACMD to consider the potential benefits of an expedited (but temporary) legislative procedure for harmful drugs that quickly become available on the market. The ACMD is concerned that at present the necessary processes to progress from an alert of a harmful drug through to legislation under the Misuse of Drugs Act 1971 takes some considerable time, usually years. During this period there is potential time for markets of a drug to become established and for harm to be caused. Such a measure may be particularly timely given the potential increase in synthetic drugs becoming available in the next few years. Such temporary control measures are already in use in the USA and Germany.

Should you wish for further information on these matters I would welcome the opportunity to discuss them with you or your officials.

Yours sincerely,



Professor David Nutt FMed Sci

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

Member	Sector
Professor David Nutt (FMedSci), Chair	Professor of Neuropsychopharmacology Imperial College London
Dr Dima Abdulrahim	Briefings Manager, National Treatment Agency
Lord Victor Adebowale	Chief Executive, Turning Point
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 Simon Campbell (CBE)	Formerly Head of Worldwide Discovery, Pfizer
Mr Eric Carlin	Chief Executive, Mentor UK
Ms Carmel Clancy	Principal Lecturer in Mental Health and Addictions, 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
Mr Patrick Hargreaves	Adviser for Drugs and Alcohol, Durham County Council, Children and Young People's Services
Ms Caroline Healy	National Adviser for the commissioning of mental health services for children in secure settings, Department of Health
Dr Matthew Hickman	Reader in Public Health and Epidemiology, Department of Social Medicine, University of Bristol
Professor Leslie Iversen (FRS)	Professor of Pharmacology, Oxford University
Dr Leslie King	Adviser to the Department of Health and the European Monitoring Centre for Drugs and Drug Addiction

Mr David Liddell	Director, Scottish Drugs Forum
Dr John Marsden	Reader in psychology, Institute of Psychiatry (Adviser to the World Health Organisation and United Nations)
Mr Peter Martin (CBE)	Independent Consultant in Substance Misuse
Dr Fiona Measham	Senior Lecturer in Criminology, Lancaster University
Ms Anita Nolan	Consultant in oral medicince, Dundee Dental Hospital and School
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
Dr Ian Ragan	Pharmaceutical industry consultant (Head of European Scientific Affairs at Eli Lilly, Executive Director of the European Brain Council)
DCC Howard Roberts	Deputy Chief Constable, Nottinghamshire Police
Dr Mary Rowlands	Consultant psychiatrist in substance misuse, Exeter
Dr Polly Taylor	Veterinary Surgeon, Cambridgeshire
Ms Monique Tomlinson	Freelance Consultant in Drugs Misuse
Mrs Marion Walker	Clinical Director, Substance Misuse Service, Berkshire Healthcare NHS Trust
Mr Arthur Wing	Assistant Chief Officer – Sussex Probation Area