ACMD

Advisory Council on the Misuse of Drugs

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Sarah Newton MP
Minister for Vulnerability, Safeguarding and Countering Extremism
Home Office
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16 December 2016

Dear Minister,

Re: ACMD Report - Phytocannabinoids

On 27 April 2016 I wrote to the then Home Secretary outlining the annual work programme for the Advisory Council on the Misuse of Drugs (ACMD). This included a new working group to review the generic definition for plant cannabinoids (*phytocannabinoids*) in the Misuse of Drugs Act 1971 (MDA).

This work followed the 2013 commission from the Home Office to the ACMD to keep under review the generic definitions in the Act and an appreciation that the literature available on the psychoactivity of phytocannabinoids has increased since the definition was first conceived.

We are pleased to inform you that this work has now been completed and provide the attached report as a presentation of our findings.

Key Findings

- A review of the literature has found that 97 phytocannabinoids have been identified so far.
- Under the agreed interpretation of the generic definition, 12 of these phytocannabinoids would be considered controlled under the MDA.

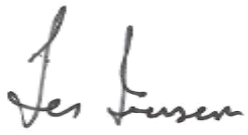
- There is sufficient evidence available for three of these controlled phytocannabinoids to conclude that they are psychoactive.
- There is one controlled phytocannabinoid (*delta-9-tetrahydrocannabinol-C3, THCV*) for which there is conflicting evidence of limited psychoactivity.
- For the remaining eight controlled phytocannabinoids, there was insufficient evidence available to determine psychoactivity or the absence thereof.

Recommendation

- The limitations upon research perceived and/or produced by inclusion of compounds in Schedule 1 of the Misuse of Drugs Regulations (2001) be reviewed to determine whether specific recommendations can be made to safely reduce or remove such limitations and so facilitate research.

We would welcome the opportunity to discuss these findings and the recommendation.

Yours sincerely,



Professor Les Iversen
Chair of ACMD

Professor Ben Whalley
Chair of Phytocannabinoids Working Group

Cc Rt. Hon. Amber Rudd MP, Home Secretary
Rt. Hon. Jeremy Hunt, MP, Secretary of State for Health
Nicola Blackwood MP, Parliamentary Under Secretary of State for Public Health

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Advisory Council on the Misuse of Drugs

Phytocannabinoids

A review of the generic definition

December 2016

Contents

1.0 Introduction

1.1. Cannabinol and 'Cannabinol derivatives' are controlled by the Misuse of Drugs Act 1971 as Class B drugs (Schedule 2, Part II, paragraph 1(a)) and the meaning of *'Cannabinol derivatives'* is defined by the following generic definition in Schedule 2, Part IV:

1.2. "*Cannabinol derivatives means 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*".

1.3. The aim of the generic definition was to include compounds named in the United Nations Convention on Psychotropic Substances 1971, specifically: "*tetrahydrocannabinol, the following isomers and their stereochemical variants: 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol, (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol, (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol, (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H- dibenzo[b,d]pyran -1- ol, 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol, (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene- 3-pentyl-6H-dibenzo[b,d]pyran-1-ol*".

1.4. Furthermore, the 2008 amendment to the Misuse of Drugs Act 1971 (SI 2008/3130) which transferred cannabinol, cannabinol derivatives, cannabis and cannabis resin from Class C to Class B continued the control of "*any ester or ether of cannabinol or of a cannabinol derivative*".

1.5. The Misuse of Drugs Act 1971 also includes all stereoisomers of controlled drugs.

1.6. In 2013 and, later, in 2015, the fact that the generic definition makes the cannabis component, delta-9-tetrahydrocannabinol-C3 (delta-9-tetrahydrocannabivarin; THCV) a controlled substance was brought to the Minister's attention. However, sufficient *in vitro* and *in vivo* evidence describing THCV's pharmacology has been published to suggest that THCV's psychoactivity may be questionable (Hill et al., 2010; Rezpa et al., 2015). Furthermore, THCV's inclusion in Schedule 1 of the Misuse of Drugs Regulations can limit research on this substance which has shown potential as a therapeutic agent.

1.7. The ACMD Chair advised the Minister that the ACMD would review all the phytocannabinoids (plant cannabinoids) so far identified to see which are

controlled under the generic definition and whether the available scientific data justifies their current control under the Misuse of Drugs Act 1971.

2.0 Interpretation of the generic definition

2.1. Prior to considering which cannabinoids known to be present in cannabis are controlled, the generic definition was evaluated in order to define criteria for phytocannabinoid inclusion or exclusion.

2.2. The term *derivative* is not defined in the MDA 1971. It is accepted that a derivative should contain the same core skeleton as the parent compound and that compound A is a derivative of compound B only if B can be converted to A in a single chemical reaction, even if such a reaction is only achievable in a theoretical sense (King, 2009). More recently it has been argued that the scope of the term *derivative* could be extended to include compounds formed by more than one chemical reaction (King et al., 2014). However, the latter view is not supported by the ACMD in relation to the use of the term *derivative* in the Misuse of Drugs Act 1971.

2.3. The term *homologue* is also not defined in the Misuse of Drugs Act 1971. A homologue is usually used to describe a compound belonging to a series of compounds differing from each other by a repeating unit, in this case a methylene (CH_2) group. The phrase *3-alkyl homologues of cannabinol* is therefore taken to mean both higher and lower homologues of cannabinol and also branched chain alkyl groups.

2.4. Finally, the phrase *tetrahydro derivatives of cannabinol*, is taken to mean the derivative is formed by the addition of four hydrogen atoms to the cannabinol structure, in a single chemical reaction whether practical or theoretical in nature. Whilst it is recognised that this phrase could possibly be interpreted as meaning derivatives of tetrahydrocannabinol compounds (by analogy with bromo-LSD in reference to King et al. (2014)), it is not an interpretation supported by the ACMD.

2.5. Compounds were therefore considered controlled if they contained:

a) The dibenzopyran ring structure present in cannabinol.
b) Four hydrogens added to the ‘C’ ring, consistent with the statement ‘tetrahydro derivatives’*
c) Any alkyl group in the 3-position of the dibenzopyran ring structure of cannabinol or a tetrahydrocannabinol compound.

*Compounds with four hydrogens on the ‘A’ (phenol) ring are included but such compounds do not occur in cannabis.

3.0 Phytocannabinoids considered

3.1. A complete list of phytocannabinoids so far identified in the plant was provided by Dr Mohamed Radwan (University of Mississippi, USA) and Professor Mahmoud ElSohly (University of Mississippi, USA), who have dedicated large parts of their careers to identifying these compounds. The list was cross checked against results obtained from a search for 'cannabinoid' made via the Dictionary of Natural Products (accessed 10/02/2016) to verify completeness.

3.2. A review of these 97 phytocannabinoids (*Appendix 1*), revealed 12 (**Figures 1-3**) which met the criteria described above and so are controlled by the MDA, 1971.

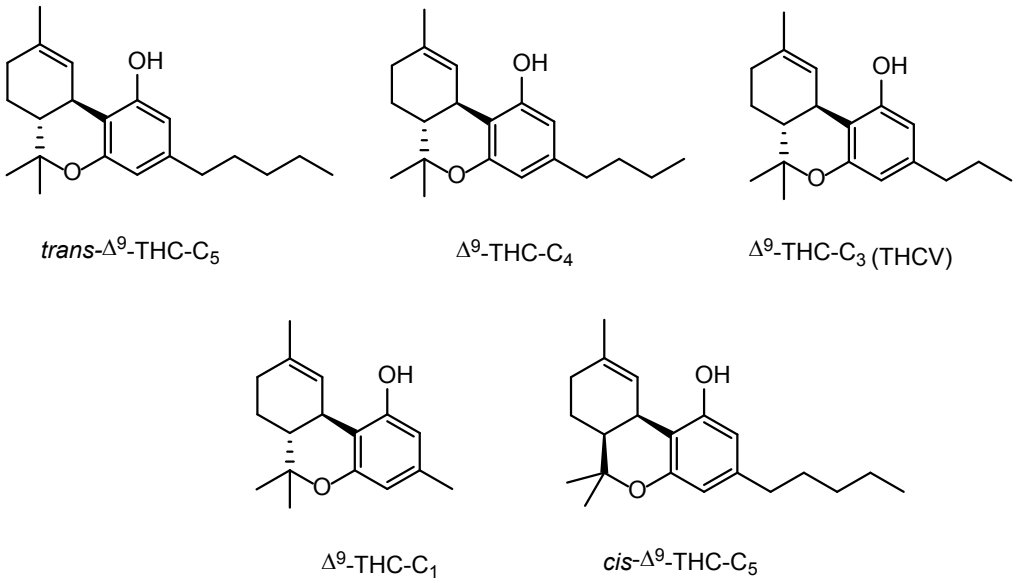

Figure 1. Δ^9-THC type phytocannabinoids controlled by the generic definition in the Misuse of Drugs Act, 1971.

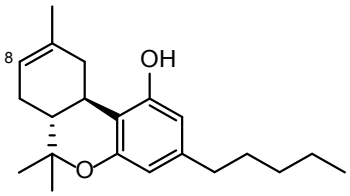

Figure 2. The Δ^8-THC type plant cannabinoid controlled by the generic definition in the Misuse of Drugs Act, 1971.

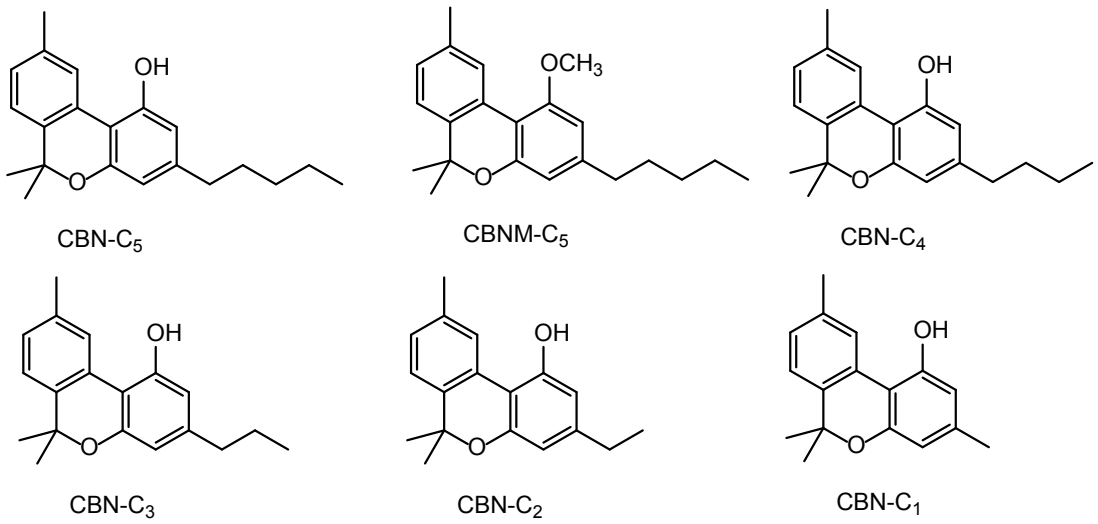

Figure 3. Cannabinol (CBN) type phytocannabinoids either explicitly named or controlled by the generic definition in the Misuse of Drugs Act, 1971.

4.0 Consideration of controlled phytocannabinoid pharmacology

4.1. Searches of the available literature using PubMed were conducted for each of the controlled phytocannabinoids in order to assess the existence of pharmacological evidence to demonstrate a presence or lack of psychoactivity for each compound.[1] Each phytocannabinoid was searched for using the full name and accepted abbreviation (Figures 1-3 & Table 1).

4.2. Since Δ^9-THC's psychoactivity is mediated by activation (partial agonism) of the cannabinoid type 1 receptor, at least one peer-reviewed and published report of such effects represents the minimum acceptable evidence required to assert psychoactivity. Affinity for the cannabinoid type 1 receptor (without evidence of activation) is not considered sufficient evidence for psychoactivity since a high affinity compound may antagonise ('block') the receptor and so render the compound devoid of psychoactive effects. Thus, the minimum acceptable evidence for psychoactivity would be:

a) a competitive binding assay in which a plant cannabinoid is shown to displace a known CB_1 receptor ligand (e.g. [3H]CP55940) from human CB_1 receptors; and,

b) a functional assay (e.g. $^{[35S]}$GTPgammaS binding assay) in which the plant cannabinoid is able to activate human CB_1 receptors. Ideally, in addition to positive results in the assay types described above, corroborating behavioural (human or animal) evidence is desirable but not necessary.

[1] (http://www.ncbi.nlm.nih.gov/pubmed)

4.3. A lack of pharmacological evidence showing cannabinoid type 1 receptor activation is not considered a justification for recommending exception of a compound from control. However, clear evidence showing that a given controlled phytocannabinoid does not activate CB_1 receptors, or an absence of psychoactive effects in relevant animal species or humans, is considered a justification for recommending an exception from control.

4.4. The pharmacological evidence considered and a summary of findings are provided in *Appendix 2*.

5.0 Results & Discussion

5.1. Consideration of the evidence for each compound based upon the criteria above informed the following key findings and recommendations:

Controlled plant cannabinoid	**Sufficient evidence available to determine psychoactivity (Y/N)**	**Psychoactive (Y/N)**	**Recommendation**
Trans-delta-9-tetrahydrocannabinol-C5	Y	Y	Remain controlled
Cis-delta-9-tetrahydrocannabinol-C5	N	Unknown	Remain controlled
Delta-9-tetrahydrocannabinol-C4	N	Unknown	Remain controlled
Delta-9-tetrahydrocannabinol-C3 (Delta-9-tetrahydrocannabivarin)	Uncertain	Unclear	Remain controlled – not appropriate to reschedule to Schedule 2 of MDR
Delta-9-tetrahydrocannabinol-C1	N	Unknown	Remain controlled
Delta-8-tetrahydrocannabinol	Y	Y	Remain controlled
Cannabinol-C1	N	Unknown	Remain controlled
Cannabinol-C2	N	Unknown	Remain controlled
Cannabinol-C3	N	Unknown	Remain controlled
Cannabinol-C4	N	Unknown	Remain controlled
Cannabinol-C5	Y	Y	Remain controlled
Cannabinol methyl ether-C5	N	Unknown	Remain controlled

Table 1: Summary of key findings for phytocannabinoids controlled by the generic definition in MDA 1971 and associated recommendations for control.

5.2. Overall, the evidence reviewed was clear: either compounds were demonstrably psychoactive or no evidence demonstrating psychoactivity could be found. However, in the case of THCV, contradictory evidence was found and so critical discussion is warranted.

5.3. Of the 17 reports describing THCV pharmacology, one (Hollister, 1974) described weak trans-delta-9-tetrahydrocannabinol-C5-like effects in 5 of 6 human participants (20-25% of the potency exhibited by trans-delta-9-tetrahydrocannabinol-C5) following intravenous administration of 7mg THCV. This finding is at odds with the *in vitro* CB_1 receptor antagonist and non-psychoactive behavioural effects reported in the 16 other reports of THCV effects reviewed. Of these 16 reports, 13 described *in vivo* studies in animals (10) and humans (3) (*Appendix 2*).

5.4. The three, recent studies of THCV in humans did not report any psychoactive effects. In one study, orally administered THCV (10mg) did not produce any psychoactive effects and was also reported to attenuate the effects of Δ^9-THC (1mg; i.v.) in ten human subjects (Englund et al., 2016). Two further human studies, each employing 20 participants, examined THCV effects upon cognitive function (Rzepa et al., 2015) and reward (Tudge et al., 2014). While both detected pharmacological effects of THCV upon behaviour, neither reported any psychoactivity. Importantly, these three studies were better powered (10-20 participants per study) than Hollister's experiment (6 participants).

5.5. When considering these reports alongside Hollister (1974), it is important to note that the more recent studies (Englund et al., 2016; Rzepa et al., 2015; Tudge et al., 2014) employed a placebo-controlled, double-blind, crossover design while Hollister (1974) appeared to employ an open label design (specific methodological detail is missing from Hollister (1974)). As such, Hollister's participants knew they were receiving an active drug treatment, increasing the likelihood of a placebo effect.

5.6. The THCV experiment described in Hollister (1974) also formed part of a larger study that examined the effects of cannabidiol, cannabinol, delta-(6, 8 or 9)-tetrahydrocannabinol-C5 and some of their metabolites in humans. Hollister reported that 10/12 cannabinoids studied exerted psychoactive effects (the psychoactivity of the majority of which has subsequently been confirmed) which, when combined with the open label/no placebo study design may have influenced the direction of any placebo effect.

5.7. The route of administration may have played a part in the contrasting reports. Hollister (1974) employed the intravenous route of administration while the more recent human studies used oral administration (Englund et al., 2016; Rzepa et al., 2015; Tudge et al., 2014). The weak psychoactive effects reported by Hollister (1974) have since been hypothetically attributed to the

effects of a 11-hydroxy-delta-9-tetrahydrocannabivarin metabolite (Pertwee, 2008) although this remains to be proved. Moreover, the size of a placebo response is greater when the intravenous route of administration is used (as compared to oral administration) (Shapiro, 1970).

5.8. Although primarily acting as an antagonist at CB_1 receptors *in vitro*, capable of blocking the effects of CB_1 agonists, and showing no psychoactive effects in recent human studies that employed oral administration, it is impossible to dismiss the findings of Hollister (1974). It is possible that THCV or one of its human metabolites may exhibit some limited dose- and/or route-dependent psychoactivity.

6.0 Conclusions

6.1. Of the 12 phytocannabinoids controlled, sufficient evidence to demonstrate psychoactivity was found for three (trans-delta-9-tetrahydrocannabinol-C5, delta-8-tetrahydrocannabinol and cannabinol-C5). There are also 8 phytocannabinoids controlled for which psychoactivity is unknown and in these cases, there is insufficient evidence to determine psychoactivity.

6.2. The majority of evidence describing the pharmacological effects of delta-9-tetrahydrocannabinol-C3 (delta-9-tetrahydrocannabivarin) suggests that it is not, in itself, psychoactive. However, this evidence could not conclusively dismiss one report of limited psychoactive effects following intravenous administration of delta-9-tetrahydrocannabinol-C3 in humans. Definitive evidence proving the presence or absence of limited dose- and/or route-dependent psychoactive effects following delta-9-tetrahydrocannabinol-C3 administration in humans remains to be reported.

6.3. In view of the residual uncertainty regarding the psychoactivity of delta-9-tetrahydrocannabinol-C3, it should remain controlled until potential risks noted above can be properly assessed by research.

6.4. While the potential risks in 6.2 appear limited, it is not appropriate to recommend rescheduling of delta-9-tetrahydrocannabinol-C3 to Schedule 2 of the Misuse of Drugs Regulations 2001, since only therapeutic (medicinal) potential, not proof, has thus far been demonstrated. Such potential can only be established by further research.

6.5. In both 6.4 and 6,5 above, the research required remains limited by delta-9-tetrahydrocannabinol-C3's continued inclusion in Schedule 1 of the Misuse of Drugs Regulations.

7.0 Recommendation

7.1. The ACMD recommends that the reasons for the limitations upon research perceived and produced by inclusion of compounds in Schedule 1 of the Misuse of Drugs Regulations (2001) be reviewed in order to determine whether specific recommendations can be made that can safely reduce or remove such limitations and so facilitate research.

The ACMD, through its Technical Committee, will review and report on these issues to Ministers in 2017.

8.0 References

Dictionary of Natural Products http://dnp.chemnetbase.com/dictionary-search.do;jsessionid=B79461ACB9F6C1BA24B7C606F2FD0FAA?method=view&id=11527596&si Accessed: 10/02/2016

Englund A, Atakan Z, Kralj A, Tunstall N, Murray R, Morrison P. 2016. The effect of five day dosing with THCV on THC-induced cognitive, psychological and physiological effects in healthy male human volunteers: A placebo-controlled, double-blind, crossover pilot trial. J Psychopharmacol. 30(2):140-51.

Hill AJ, Weston SE, Jones NA, Smith I, Bevan SA, Williamson EM, Stephens GJ, Williams CM, Whalley BJ. 2010. Δ^9-Tetrahydrocannabivarin suppresses *in vitro* epileptiform and *in vivo* seizure activity in adult rats. Epilepsia. 51(8):1522-32.
Hollister LE 1974. Structure–activity relationships in man of cannabis constituents and homologs and metabolites of Δ^9-tetrahydrocannabinol. Pharmacology. 11:3–11.

King, L. A. 2009. Forensic chemistry of substance misuse: a guide to drug control. Cambridge, UK: RSC Pub., p20-21

King, L. A., Ujváry, I., Brandt, S. D. Drug laws and the 'derivative' problem. Drug Testing and Analysis, 2014, 6, 879-883.

Pertwee RG (2008) The diverse CB_1 and CB_2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ^9-tetrahydrocannabivarin. Br J Pharmacol. 153(2): 199–215.

Rzepa E, Tudge L, McCabe C. 2015. The CB_1 Neutral Antagonist Tetrahydrocannabivarin Reduces Default Mode Network and Increases Executive Control Network Resting State Functional Connectivity in Healthy Volunteers Int J Neuropsychopharmacol. 19(2) pii: pyv092.

Shapiro AK 1970. Placebo Effects in Psychotherapy and Psychoanalysis The Journal of Clinical Pharmacology and The Journal of New Drugs 10(2): 73–78

Tudge L, Williams C, Cowen PJ, McCabe C. 2014. Neural effects of cannabinoid CB_1 neutral antagonist tetrahydrocannabivarin on food reward and aversion in healthy volunteers. Int J Neuropsychopharmacol. 18(6). pii: pyu094.

Appendix 1: Phytocannabinoids MDA Status

Name	Status		
	Not controlled	Controlled	
		Explicitly listed	Generic definition
Δ^4(8)-Isotetrahydrocannabinol	x		
Δ^4-Isotetrahydrocannabinol	x		
Δ^9-THC C_5			x
Δ^9-THCA-C_5A	x		
Δ^9-THCA-C_5B	x		
Δ^9-THC C_4			x
Δ^9-THCA-C_4A	x		
Δ^9-THCV-C_3			x
Δ^9-THCVA-C_3A	x		
Δ^9-THCO-C_1			x
Δ^9-THCOA-C_1A	x		
Cannabisol	x		
Δ^9-THCA-C_5A esters	x		
8-hydroxy-Δ^9-THC C_5	x		
11-hydroxy-Δ^9-THC C_5 ester	x		
Δ^9-THC aldehyde C_5A	x		
8-oxo-Δ^9-THC aldehyde C_5A	x		
Δ^8-THC C_5			x
Δ^8-THCA C_5A	x		
10-hydroxy-Δ^8-THC C_5	x		
10a-hydroxy-10-oxo-Δ^8-THC C_5	x		
(*E*)CBG-C_5	x		
(*E*)CBGA-C_5	x		
(*E*)CBGM-C_5	x		
(*E*)CBGAM-C_5	x		
(*E*)CBGVA-C_3	x		
(*E*)CBGV-C_3	x		
(*Z*)CBGA-C_5	x		
carmagerol	x		

(*E*)CBGA-C_5 esters	x		
sesquicannabigerol	x		
4-hydroxy-(*E*)CBG-C_5 ester	x		
(*E*)CBGA-C_5 epoxides	x		
CBC-C_5	x		
CBCA-C_5	x		
±CBCV-C_3	x		
±CBCVA-C_3	x		
CBCVA-C_3	x		
CBD-C_5	x		
CBDA-C_5	x		
CBDM-C_5	x		
CBD-C_4	x		
CBDV-C_3	x		
CBDVA-C_3	x		
CBD-C_1	x		
CBND-C_5	x		
CBND-C_3	x		
CBEA-C_5 A	x		
CBE-C_5	x		
CBEA-C_5 B	x		
CBEA-C_3 B	x		
CBE-C_3	x		
CBL	x		
CBLA	x		
CBLV	x		
CBN-C_5 (cannabinol)		x	
CBNA-C_5 [cannabinolic acid)	x		
CBNM-C_5 (cannabinol ether)		x	
CBN-C_4			x
CBN-C_3			x
CBN-C_2			x
CBN-C_1			x
CBNA-C_5 ester	x		
8-hydroxy-CBNA-C_5	x		
8-hydroxy-CBN-C_5	x		
1'-8-dihydroxy-CBN-C_5	x		

(-)-*trans*-CBT-C_5	x		
(+)-*trans*-CBT-C_5	x		
(±)-*cis*-CBT-C_5	x		
(-)-*trans*-CBT-OEt-C_5 (an ether)	x		
(±)-*trans*-CBT-C_3	x		
CBT-C_3 homologue	x		
(-)-*trans*-CBT-OEt-C_3 (an ether)	x		
8,9-di-OH-CBT-C_5	x		
CBDA-C5 9-OH-CBT-C_5-ester	x		
DCBF-C_5	x		
CBF-C_5	x		
OTHC	x		
OH-iso-HHCV-C_3	x		
CBCN-C_5	x		
CBCN-C_3	x		
Cannabicitran	x		
***cis*-Δ^9-THC**			x
CBR	x		
CBTT	x		
***cis*-iso-Δ^7-THCV**	x		
***trans*-iso-Δ^7-THCV**	x		
***trans*-iso-Δ^7-THC**	x		
CBM	x		
CBX	x		
10-hydro-$\Delta^{9,11}$-THC	x		
Δ^9-THC epoxide	x		
9-hydroxy-hexahydrocannabinol	x		
9-hydroxy-7-oxo-hexahydrocannabinol	x		
10-hydroxy-hexahydrocannabinol	x		
10a-hydroxy-hexahydrocannabinol	x		
9-hydroxy-10-oxo-$\Delta^{6a,10a}$-THC	x		

Appendix 2: Summary of pharmacological effects of phytocannabinoids

Cannabinoid	Pubmed URL	*In vivo*/ *in vitro*	Species	Aim/ model	Outcome	Relevance to assessment of psychoactivity	Notes
Delta-9-tetrahydrocannabinol-C3 (delta-9-tetrahydrocannabivarin)	http://www.ncbi.nlm.nih.gov/pubmed/26577065	*In vivo*	Human	Safety and tolerability in humans	10mg p.o. indistinguishable from placebo	Suggests a lack of psychoactivity	
	http://www.ncbi.nlm.nih.gov/pubmed/26362774	*In vivo*	Human	Subjective experience and fMRI	No effect on subjective experience, detectable effect on functional connectivity in the CNS	Effect on functional connectivity not consistent with a recreational 'high'	Does detection of a CNS effect equate with 'psychoactivity'?
	http://www.ncbi.nlm.nih.gov/pubmed/25542687	*In vivo*	Human	Effects of treatment on rewarding and aversive stimuli using fMRI	Treatment increased responses to rewarding and aversive stimuli	Results indicate a CNS effect	Does detection of a CNS effect equate with 'psychoactivity'?
	http://www.ncbi.nlm.nih.gov/pubmed/25363799	*In vivo*	Rat	Phencyclidine-induced schizophrenia	Reduced stereotyped behaviour, decreased time spent immobile in the forced swim test and normalized hyperlocomotor activity, social behaviour and cognitive performance.	Results indicate a CNS effect	Does detection of a CNS effect equate with 'psychoactivity'?

Cannabinoid	Pubmed URL	*In vivo*/ *in vitro*	Species	Aim/ model	Outcome	Relevance to assessment of psychoactivity	Notes
	http://www.ncbi.nlm.nih.gov/pubmed/25257544	*In vitro* & *in vivo*	Human and non-human	Meta-analysis/systematic review of pharmacological data	High-affinity CB_1 receptor antagonist *in vitro* but produces only limited effects *in vivo* that arise from CB_1 antagonism. Also a partial agonist at CB_2 receptors.	Results demonstrate a) lack of CB_1 agonism and b) limited functional effects as a CB_1 antagonist.	Most robust (systematic review) evidence that THCV does not act as a CB_1 agonist.
	http://www.ncbi.nlm.nih.gov/pubmed/23902479	*In vivo*	Rat	Comparison of THCV with known CB_1 antagonists/inverse agonist effects on nausea	CB_1 antagonists/inverse agonists produce nausea, THCV did not. THCV does not have a behavioural profile consistent with CB_1 inverse agonism/antagonism.	Results show THCV has limited functional effects as a CB_1 antagonist.	
	http://www.ncbi.nlm.nih.gov/pubmed/23712280	*In vivo*	Mouse	Dietary- and genetically induced obesity in mouse models: THCV compared with the CB_1 antagonist, AM251	Differential effects of THCV vs AM251 suggesting a distinct pharmacology	Results show THCV has limited functional effects as a CB_1 antagonist.	
	http://www.ncbi.nlm.nih.gov/pubmed/23103902	*In vivo*	Rat	Comparison of THCV and the CB_1 antagonist rimonabant in a model of anxiety	THCV not anxiogenic, unlike rimonabant.	Results show THCV has limited functional effects as a CB_1 antagonist.	
	http://www.ncbi.nlm.nih.gov/pubmed/21796370	*In vivo*	Rat and mouse	Plasma and brain PK of THCV	THCV penetrates blood brain barrier	No functional effects assessed.	THCV is able to reach the central nervous system in rodents.

Cannabinoid	Pubmed URL	*In vivo*/ *in vitro*	Species	Aim/ model	Outcome	Relevance to assessment of psychoactivity	Notes
	http://www.ncbi.nlm.nih.gov/pubmed/21726418	*In vitro*	Human	Effects of THCV on TRPV channels	THCV stimulates TRPV3 and TRPV4 channels	Targets not known to produce psychoactive effects.	
	http://www.ncbi.nlm.nih.gov/pubmed/20196794	*In vitro* and *in vivo*	Rat	Effects of THCV on *in vitro* epileptiform activity and *in vivo* seizures. Radioligand binding.	THCV reduces epileptiform activity *in vitro* and *in vivo*. THCV acts as a CB_1 antagonist in radioligand binding studies.	CB_1 antagonists are pro-convulsant which makes findings suggest that THCV has limited functional effects as a CB_1 antagonist.	
	http://www.ncbi.nlm.nih.gov/pubmed/18493244	*In vitro*	Mouse	Radioligand binding	THCV acts as a CB_1 receptor antagonist.		
	http://www.ncbi.nlm.nih.gov/pubmed/18311186	*In vitro*	Mouse	*In vitro* slice electrophysiology	THCV acts as a functional CB_1 receptor antagonist *in vitro*.		

Cannabinoid	Pubmed URL	*In vivo*/ *in vitro*	Species	Aim/ model	Outcome	Relevance to assessment of psychoactivity	Notes
	http://www.ncbi.nlm.nih.gov/pubmed/17828291	*In vitro* and *in vivo*	Non-human	Review of evidence on THCV to 2008.	THCV is a potent CB_2 receptor partial agonist *in vitro*. THCV antagonizes CB agonists in CB_1-expressing tissues with relatively high potency and tissue and ligand dependent manner. *In vivo*, THCV interacts with CB_1 receptors as a CB_1 antagonist or, at higher doses, as a CB_1 receptor agonist	Suggestion of effects as a CB_1 receptor agonist at high doses *in vivo*.	High dose effects *in vivo* could be psychoactive.
	http://www.ncbi.nlm.nih.gov/pubmed/17245367	*In vitro* and vivo	Mouse	Radioligand binding and *in vivo* testing vs D9-THC	THCV acts as a CB_1 antagonist *in vitro* and can antagonise the effects of D9-THC *in vivo*.	Results show THCV can exert functional effects as a CB_1 antagonist.	
	http://www.ncbi.nlm.nih.gov/pubmed/4610598	*In vivo*	Human	i.v. administration of several isolated phytocannabinoids in human volunteers and assessment of subjective effects	In 5/6 subjects, 7mg i.v. THCV reportedly produced mild to moderate effects similar to those reported for THC.	Suggests psychoactivity	See main report for limitations of study.

Cannabinoid	Pubmed URL	*In vivo/ in vitro*	Species	Aim/ model	Outcome	Relevance to assessment of psychoactivity	Notes
	http://www.ncbi.nlm.nih.gov/pubmed/16205722	*In vitro*	Mouse	Radiioligand binding	THCV acts as a CB_1 antagonist		
Trans-delta-9-tetrahydrocannabinol-C5	Gaoni Y & mechoulam R (1964) Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish J. Am. Chem. Soc. 86 (8) 1646–1647	*In vivo*	Dog	Behavioural assessment	First demonstration of psychoactivity caused by THC – effects of cannabis consumption on dogs reproduced with THC alone.		More detailed report of psychoactive effects described in: http://www.ncbi.nlm.nih.gov/pubmed/4981896
Cis-delta-9-tetrahydrocannabinol-C5	http://www.who.int/medicines/areas/quality_safety/4.2DronabinolCritReview.pdf	N/A	N/A	N/A	N/A	N/A	Only reference to this isomer that I can find but no mention of pharmacology made.
Delta-9-tetrahydrocannabinol-C4	https://www.ncbi.nlm.nih.gov/pubmed/6715	N/A	N/A	N/A	N/A	N/A	Describes identification but no evidence of pharmacology found.
Delta-9-tetrahydrocannabinol-C1	No evidence found						

Cannabinoid	Pubmed URL	*In vivo*/ *in vitro*	Species	Aim/ model	Outcome	Relevance to assessment of psychoactivity	Notes
Delta-8-tetrahydrocannabinol	http://www.ncbi.nlm.nih.gov/pubmed/4788032	*In vivo*	Mouse	Antinociception and gastric motility	D8-THC behaved comparably to D9-THC	Results suggest a similar pharmacology	Similar effects of CBN also reported.
	http://www.ncbi.nlm.nih.gov/pubmed/810346	*In vivo*	Baboon	Kindled seizures	D8-THC behaved comparably to D9-THC – anticonvulsant and similar toxicity (i.e. central effects) profiles.	Results suggest a similar pharmacology and central symptom suggests blood brain barrier penetration. Similarity to D9-THC suggests psychoactivity.	
	http://www.ncbi.nlm.nih.gov/pubmed/6247159	*In vivo*	Mouse	Hypothermia, catalepsy, extension of phenobarbital-induced sleeping time	While not directly compared in the study, D8-THC's effects were comparable to those reported for D9-THC in the same tests	Results suggest a similar pharmacology and central symptom suggests blood brain barrier penetration. Similarity to D9-THC suggests psychoactivity.	
	http://www.ncbi.nlm.nih.gov/pubmed/2892923	*In vivo*	Mouse	Sleep prolongation and interaction with barbiturates	D8-THC exerts sedative CNS effects	Results suggest psychoactivity of D8-THC and primary (hydroxyl) metabolite.	

Cannabinoid	Pubmed URL	*In vivo/ in vitro*	Species	Aim/ model	Outcome	Relevance to assessment of psychoactivity	Notes
	http://www.ncbi.nlm.nih.gov/pubmed/2177683	*In vivo*	Mouse	Catalepsy, hypothermia, pentobarbital-induced sleep prolongation, anticonvulsant and analgesic effects	Comparable effects to D9-THC although less potent	Psychoactive	
	http://www.ncbi.nlm.nih.gov/pubmed/11159703	*In vitro*	Rat	Radioligand binding	D8-THC acts as a CB1 agonist *in vitro*.		
Cannabinol-C1	No evidence found						
Cannabinol-C2	No evidence found						
Cannabinol-C3	No evidence found						
Cannabinol-C4	No evidence found						
Cannabinol-C5	http://www.ncbi.nlm.nih.gov/pubmed/3035413	*In vivo*	Rat & pigeon	Behavioural assessment	CBN-C5 produces the same behavioural effects as D9-THC (comparator control) although with lower potency.	Psychoactive	
	http://www.ncbi.nlm.nih.gov/pubmed/25311884	*In vitro*	Recombinant – species not stated	Radioligand binding (affinity)	CBN-C5 shows nM affinity for CB_1 receptors.	Binding to receptor target consistent with psychoactivity.	

Cannabinoid	Pubmed URL	*In vivo*/ *in vitro*	Species	Aim/ model	Outcome	Relevance to assessment of psychoactivity	Notes
	http://www.ncbi.nlm.nih.gov/pubmed/9580597	*In vitro*	Rat	Radioligand binding in high (100uM) GDP conditions	CBN-C5 and D9-THC behave similarly and are unable to overcome GDP block.	No useful conclusions about psychoactivity	
	http://www.ncbi.nlm.nih.gov/pubmed/7728937	*In vivo*	Mice	Catalepsy, hypothermia, pentobarbital-induced sleep prolongation, anticonvulsant effects.	CBN-C5 produces effects similar to those reported for D9-THC in the same tests/species.	Psychoactive	
Cannabinol monomethyl ether-C5	No evidence found						

Appendix 3: Contributions to this review

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