ACMD

Advisory Council on the Misuse of Drugs

Cumyl-PeGaClone and other recently encountered synthetic cannabinoid receptor agonists

A review of the evidence on their use and harms

Contents

1. Introduction

1.1. Synthetic cannabinoid receptor agonists (SCRA), sometimes referred to as synthetic cannabinoids, are chemicals that exert psychoactive effects by stimulating the same receptors within the body that are responsible for mediating the pharmacological effects of tetrahydrocannabinol (THC), the major active ingredient of cannabis. The ACMD has previously provided several reports on this group of compounds, including most recently an updated harms assessment published in October 2020. [ACMD, 2020a].

1.2. The pharmacology of SCRA is complex and was reviewed in our recent harms assessment. Briefly, SCRA act via both type 1 and type 2 cannabinoid (CB_1 and CB_2) receptors; but their stimulation of CB_1 receptors in the brain is thought to be primarily responsible for their psychoactive effects. Common modes of use include smoking of herbal mixtures impregnated with pure SCRA compound, vaporising ('vaping') SCRA liquid solutions using e-cigarettes or ingestion of SCRA-containing pills, powders, edible 'gummies' or impregnated paper. In recent years, use of SCRA has been most prevalent amongst homeless people and in prisons.

1.3. Use of SCRA can produce important adverse health effects including confusion, anxiety, agitation, psychosis, vomiting, reduced level of consciousness with impaired ventilation and loss of airway reflexes, cardiac dysrhythmias, seizures, and liver or kidney failure. These effects may cause hospitalisation and in severe cases death may occur. Withdrawal effects are also reported after discontinuation of use. Further details of the health and social harms associated with SCRA use are provided in our previous report.

1.4. The ACMD has previously advised that legislation controlling most SCRA under the Misuse of Drugs Act (MDA) 1971 and the Misuse of Drugs Regulations (MDR) 2001 should be based on generic definitions of their chemical structures, although there are also some substances listed individually by name. Generic definitions describe a range of chemical structures that are subject to control. They were recommended because the complexity of SCRA molecules allow numerous opportunities for manufacturers to make small modifications to part of the molecule to produce a new substance that evades legal controls based on the listing of individual compounds. The original generic definition was recommended by the ACMD in 2009, but following further ACMD advice was broadened in 2012 and again in 2016. The definition was further adjusted in 2019 to remove some legitimate compounds that were unintentionally caught by the 2016 definition. Compounds captured by the current UK definition are controlled as Class B under the MDA 1971 and placed under Schedule 1 of the MDR 2001. This classification and scheduling was most recently endorsed by the ACMD in its 2020 report. [ACMD, 2020a]. Substances outside the scope of the MDA but which are shown to produce psychoactive effects are subject to the provisions of the Psychoactive Substances Act (PSA) 2016.

1.5. Most seized SCRA material is believed to originate from China and there is evidence that legal control measures enacted in that country have had a

substantial effect on the compounds detected internationally [Copeland et al, 2022; Craft et al 2022; Andrews et al 2022]. China enacted new legislation to control SCRA as a class using seven commonly encountered structural backbones in July 2021, but since then a number of new SCRA have emerged with chemical core components that appear to have been designed with the intention of avoiding evolving international and national legal controls, including this recent Chinese legislation. Many of the new structural variants have been derived from materials previously described in published pharmaceutical research and patents as having activity at the cannabinoid receptors.

1.6. One of these newer compounds, Cumyl-PeGaClone, has been reviewed by the World Health Organization. [WHO, 2020] Following this, the United Nations Commission on Narcotic Drugs has recommended its addition to Schedule II of the Convention on Psychotropic Substances 1971. As this obliges the UK, as a signatory, to introduce appropriate legal control measures, the Home Secretary has asked the ACMD to provide advice on the appropriate domestic controls for Cumyl-PeGaClone under the MDA 1971, the MDR 2001 and, where appropriate, the Misuse of Drugs (Designation) Order 2015.

1.7. This document, therefore, reviews the evidence of use and harms of SCRA, including Cumyl-PeGaClone, that have been detected recently in illicit markets in the UK or internationally, but that are also not currently controlled via the MDA 1971 (‘uncontrolled SCRA’). It considers whether these compounds merit control under the MDA, rather than the Psychoactive Substances Act, and whether such changes could be effected by means of extensions of the existing generic controls, rather than by making substance-specific entries.

2. Uncontrolled SCRA detected internationally and in the UK

2.1. The SCRA that fall outside the current UK generic control that have been detected internationally and in the UK up to September 2022 are listed in Annex A, which also summarises available information on chemistry, pharmacology and health harms. Limited evidence of cannabinoid receptor activity is available for some compounds, although potency varies. There is also very limited information available on health harms associated with use of these specific compounds; some have been identified in samples from those with severe or fatal toxicity, but often alongside other substances, so the contribution of the SCRA to the clinical effects may be uncertain. It seems likely, however, that health harms of use of emerging compounds with CB_1 receptor potency will be similar to those of established SCRA

2.2. UK data provided in this report comes from responses to data requests made by the ACMD in June and November 2022 for detections reported by forensic laboratories or coroners (e.g., Eurofins, FEWS/DSTL, EU-MADNESS), after analysis of drug seizures, including from prisons (e.g., OHID, NCA), voluntary donations of drug samples (e.g., WEDINOS) or detections in research study participants with drug toxicity attending emergency departments (e.g., IONA). Analysis is not undertaken as part of routine medical care, so routine hospital admission and poisons centre data are of very limited value in detecting specific novel compounds. Similarly, mortality data are not routinely reported for specific SCRA in the UK, including the devolved administrations. No detections of the uncontrolled SCRA listed in Annex A were reported by Border Force, TICTAC Communications Ltd, the NPSAD study or the EU-MADNESS project. Note that acronyms used in this paragraph and elsewhere in the report are explained in Annex B.

2.3. Whilst all the compounds listed in Annex A have been identified in drug markets internationally over the last decade, QMPSB, M-CHMIC and all the carbazole core compounds have not been encountered recently. Similarly, within the ɣ-carbolin-1-one (2,5-dihydro-1*H*-pyrido[4,3-b]indol-1-one) core compounds, there has been some evolution with time from Cumyl-PeGaClone to other variants including most recently Cumyl-CB-MeGaClone and Cumyl-NB-MeGaClone.

2.4. The uncontrolled SCRA detected (confirmed or provisional detections) in the UK as reported for this review include one ɣ-carbolin-1-one core compound (5F-Cumyl-PeGaClone), all five of the listed “Oxizid” (referring to the oxoindole core and the hydrazide linker) compounds (BZO-HEXOXIZID, BZO-POXIZID , BZO-4en-POXIZID, BZO-5F-POXIZID and BZO-CHMOXIZID), four of the “acetamide-linked” compounds (ADB-FUBIACA, ADB-IACA, CH-PIACA and A-FUBIACA) and 2 ‘no-tail’ compounds (ADB-5Br-INACA, MDMB-5Br-INACA). There have also been previous detections of MDMB-CHMCZA, but not since 2016. There are no reports of detections of any other substances listed in Annex A in the UK, including Cumyl-PeGaClone. Importantly, the great majority of SCRA currently being detected in the UK continue to be captured by the current generic definition, with the most prevalent since 2020

being MDMB-4en-PINACA, ADB-BUTINACA and AB-PINACA. In interpreting this information, it should be noted that current methods of surveillance used in the UK are likely to underestimate the involvement of new compounds as these may not be detected by the standard analytical methods used.

2.5. The majority of the novel SCRA encountered internationally that are outside the scope of the current UK generic SCRA controls fall into the following structural groupings (Annex A):

a) Materials with a carbazole or ɣ-carbolin-1-one core. In each of these groups, the same types of 'tail' structures and linked groups which have been seen in earlier generations of SCRA are attached to the new cores. Both of these cores were included in the Chinese generic SCRA controls introduced in 2021 and further variants are no longer being reported.

b) Materials with an acetamido linking group. These feature the same ranges of cores, linked groups and 'tails' previously seen in SCRA structures. These are being encountered in the UK.

c) “Oxizid” materials, featuring a 2-oxo-indane core with a benzohydrazide group attached at the 3- position of the indane. The “Oxizid” structure represents a combination of a core, linking and linked group, which then has the familiar range of SCRA 'tail' components at the 1- position. These are also being encountered in the UK.

d) Materials with a 'tail' structure incorporating a sulfonyl group. In the examples seen to date, the sulfonyl group is attached at the usual position for 'tail' groups and is then extended by a piperidine ring, cyclohexyl ring or a tolyl (4-methylphenyl) structure. Early indications are that these materials are not particularly potent and may be thermally unstable and therefore unsuitable for use in smoking materials. These have not been identified in the UK.

e) A further recently emergent group, referred to here as the 'no tails', consist of already known SCRA structures minus the 'tail' component of the four-part SCRA structure specified in the current UK generic control. There is a lack of published information on their cannabinoid agonist potency: loss of the tail group may reduce potency, but unpublished data suggests that some of these at least (e.g. the curtailed Br-INACA compounds such as MDMB-5Br-INACA) do have some cannabinoid receptor activity and there is the possibility that higher doses could be used in herbal and other drug preparations to make up for any reduction in potency. Consistent with this, they are being encountered in the UK in herbal smoking mixtures, although data on doses involved is not yet available. They have also been marketed as uncontrolled precursors that can be sold and then ‘finished’ locally in one step to produce high-potency SCRA, in some cases with instructions on how this can be done.

f) Materials with a methylnorbornyl 'tail'. This structure is not specifically listed in para 1(ca)(ii) of the current generic control and there is potentially ambiguity over whether materials containing it fall within its scope (see below). g) A number of other SCRA structures have been reported internationally, such as a material with a hydroquinoline core, and another with a thiazole linking group, but these materials do not appear to be prevalent and have not been reported in the United Kingdom.

3. Legitimate use

3.1. Potential therapeutic roles have been proposed for some of the compounds listed in Annex A. For example, “carbazole core” compounds have been investigated for possible analgesic effects and a patent applied for [Diaz et al., 2012; Gadotti et al., 2013]. There has also been speculation that BZO-HEXOXIZID could have therapeutic efficacy for treating neuropathic pain [Xu et al., 2010] and this compound has also been shown to have anti-tumour activity, specifically for hepatocellular carcinoma [Rao et al., 2019] and melanoma [Dang et al., 2018].

3.2. The Medicines and Healthcare products Regulatory Agency (MHRA) have, however, not been able to identify clinical trials currently being conducted in the UK involving any of the compounds listed in Annex A.

4. Summary and conclusions

4.1. Compounds that have (or are likely to have) cannabinoid receptor agonist activity and that are not controlled via the MDA 1971 have been identified in illicit drug markets internationally; several of these have also been identified in the UK.

4.2. One of the listed uncontrolled SCRA, Cumyl-PeGaClone, has been added to Schedule II of the Convention on Psychotropic Substances 1971 so the UK is obliged to introduce control measures, although detections of this compound have not been reported in the UK.

4.3. Control of the other SCRA listed in Annex A should also be considered, with the priorities being higher potency compounds and those recently identified in the UK.

4.4. Some compounds listed in Annex A have been sold as precursors, sometimes with instructions on how to convert these to other SCRA, but they are also sold as final products so it is considered appropriate to control of these via the MDA 1971 rather than via precursor legislation.

4.5. In light of the continuing emergence of New Psychoactive Substances (NPS) including SCRA, there is a need to improve surveillance of compounds involved in episodes of severe toxicity or deaths. The ACMD has previously recommended that a working group should be established to consider and provide recommendations on a UK-wide minimum standard set of post-mortem toxicology tests for apparent drug-related deaths, to include testing for relevant NPS to improve consistency of analysis and detection.

5. Options for control

5.1. SCRA that are captured by the current generic definition in the MDA 1971 are listed as Class B compounds and, having no recognised medicinal value, appear in Schedule 1 of the MDR 2001. The options for control of the SCRA listed in Annex A that fall outside the current generic definition are as follows:

(a) Control only cumyl-PeGaClone; the UK is obliged to do this by our national obligations under the UN Convention on Psychotropic Substances 1971.

Other SCRA listed in Annex A would not be controlled via the MDA but for those with CB1 receptor agonist properties, it is already an offence to produce, supply, offer to supply, possess with intent to supply, possess on custodial premises, import or export under the PSA 2016. The position of these SCRA, however, would not be consistent with those already covered by the current generic.

(b) Control and scheduling of some (including Cumyl-PeGaClone) or all of the SCRA listed in Annex A via the MDA 1971 and MDR 2001 as Class B Schedule 1 compounds. This would be consistent with the position for other established SCRA. It could be achieved by

(i) Control and scheduling of specific compounds by name (including Cumyl-PeGaClone). This is a simpler and quicker option, but would risk being overtaken by the rapid development of further variants, as has been seen in other families of NPS.

(ii) Adjusting the current UK generic description to incorporate further core structures. This would ‘future-proof’ the legislation by covering known and predicted variants, at least to some extent, although further SCRA which fall outside the revised generic are likely to emerge in the future. Use of the generic approach would require consultation with stakeholders because of the risk of inadvertently including materials of legitimate pharmaceutical or wider industrial use. This would delay introducing legislation, but the numbers of detections in the UK of SCRA outside the current scope of the MDA’s controls are currently limited (although could increase).

6. Recommendation

A consultation should be undertaken with stakeholders, including academia and the chemical and pharmaceutical industries on modifications to the current generic control for SCRA, to capture currently uncontrolled SCRA that have been detected in the UK and internationally, as listed in Annex A. The proposed wording for the generic definition for addition to the MDA is provided in Annex C.

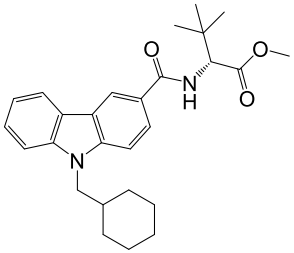
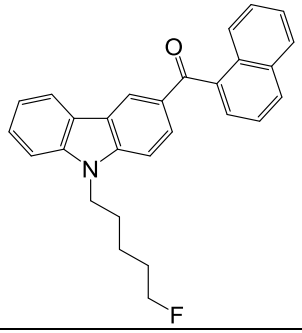
This would include Cumyl-PeGaClone, which has been added to Schedule II of the Convention on Psychotropic Substances 1971.
Compounds covered by the revised generic would, therefore, be classified as Class B compounds under the MDA 1971.

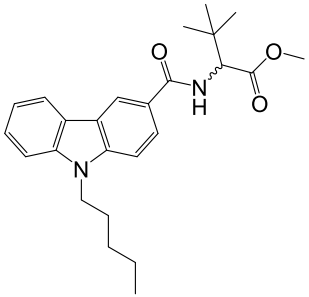
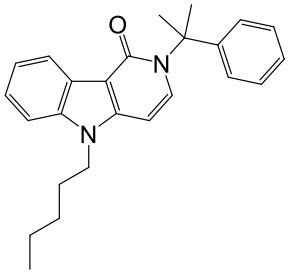
As yet, no medical use of any of these compounds has been established, so those covered by the revised generic definition should appear in Schedule 1 of the MDR 2001 (as amended) and added to schedule 1 of the Misuse of Drugs (Designation) (England, Wales and Scotland) Order 2015, to which section 7(4) of the Misuse of Drugs Act 1971 applies.

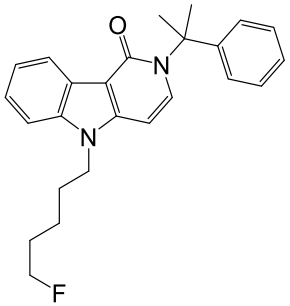
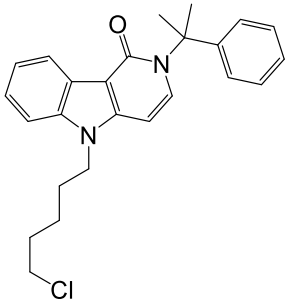
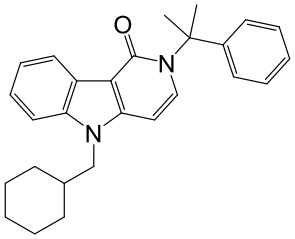
Lead: Home Office

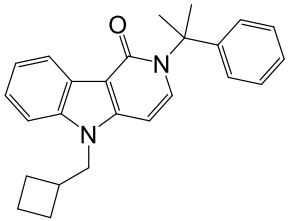
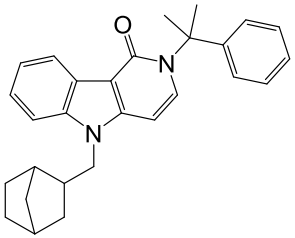
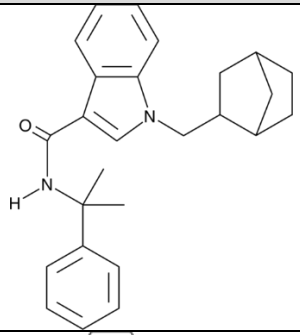
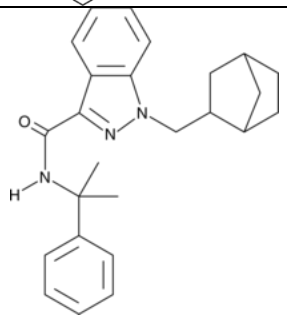
Measure of outcome: The incorporation of the revised generic descriptions into the MDA 1971 and Schedule 1 of the MDR 2001 and the Misuse of Drugs (Designation) (England, Wales and Scotland) Order 2015

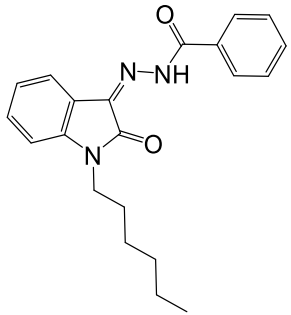
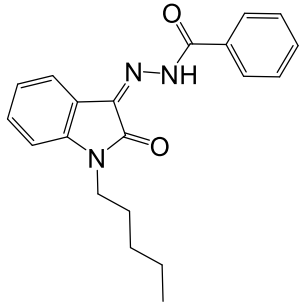
Annex A: SCRA reported internationally that are outside current UK generic control.

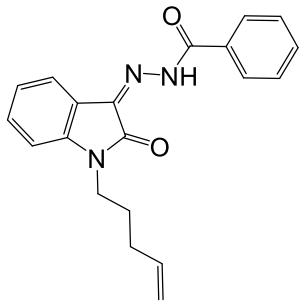
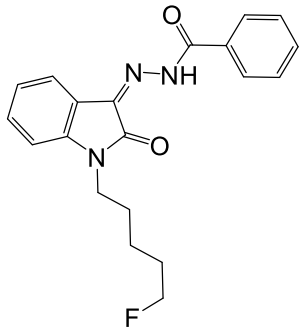
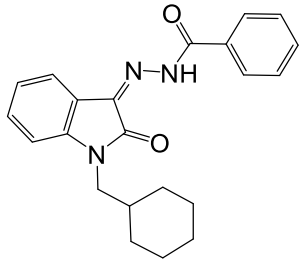
	Structure	Chemistry/ synonyms	Pharmacology	Detection and health harms	
				International	**UK**
Carbazole core					
MDMB-CHMCZCA		Carbazole analogue of MDMB-CHMICA [Mogler et al. 2018]	CB_1 receptor agonist and CB_2 receptor antagonist affinities (Ki values) at CB_1 of 5.75 nM and at CB_2 of 6.67 nM, and EC50 values of 120 nM at CB_1 and of 807 nM at CB_2 receptors in cAMP accumulation assays [Schoeder et al., 2018].	First detected in a seizure by Swedish customs in September 2015 and notified to the EMCDDA in October 2015. MDMB-CHMCZA and 30 metabolites were identified in the urine of 20 users collected between 2016 and 2018 by German and Swiss laboratories [Mogler et al., 2018].	Eurofins Forensic Services reported 13 detections of MDMB-CHMCZA between February and November 2016 from materials (including herbal materials) seized in several locations in England and Wales, including prisons. Detected in a single sample of herbal material submitted to WEDINOS in 2016.
EG-2201		5-Fluoropentyl derivative of EG-018 and a carbazole analogue of AM-2201	Binds to cannabinoid receptors with Ki values of 22.4 nM for CB_1 and 4.36 nM for CB_2, with EC50 values of 15.6 (CB_1) and 5.65 (CB_2) nM [Schoeder et al., 2018].	First identified in a drug seizure in Sweden in December 2015 and also identified in urine collected from one German or Swiss user between 2016 and 2018 [Mogler et al., 2018].	No reports of detections in the UK.

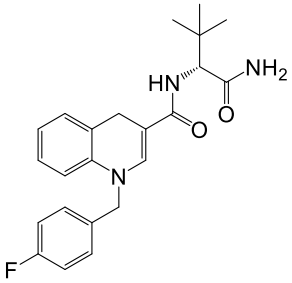
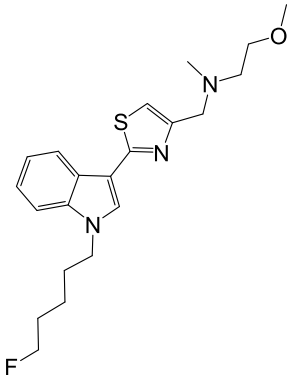
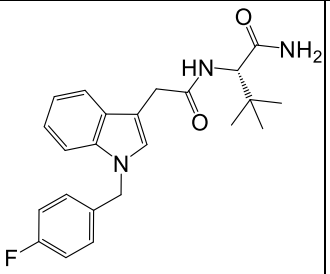
MDMB-PCZCA		Carbazole analogue of MDMB-PINACA	No information available.	First reported to the EMCDDA from Germany in May 2017 [EMCDDA–Europol, 2017].	No reports of detection in the UK.
ɣ-carbolin-1-one core					
Cumyl-PeGaClone		Cumyl and pentyl groups with a pyridoindol-1-one core. Structurally related to cumyl-PICA. [WHO, 2020]	High affinity for both CB_1 and CB_2 receptors, with similar low nanomolar affinities, coupled with high efficacy in a cAMP accumulation assay. This indicates that it is a potent, full agonist at cannabinoid receptors [Angerer et al., 2018; WHO, 2020].	First identified in herbal materials purchased in Germany in December 2016, [Angerer et al., 2018] reported to the EMCDDA - Europol in February 2017 [EMCDDA, 2017] and identified in herbal materials or e-liquids in 17 other countries by 2019. Detected in 34 samples from fatal and non-fatal cases in Germany during 2017, in a third of cases in combination with other SCRA. Six fatal cases involving Cumyl-PeGaClone were identified, but the compound was unlikely to be directly responsible for the deaths in the majority of cases [Halter et al., 2018]. Considered a significant contributor to deaths in Australia [Tiemensma et al., 2021]. Seizures reported to WHO decreased between 2018 and 2020 [WHO, 2020].	No reports of detection in the UK.

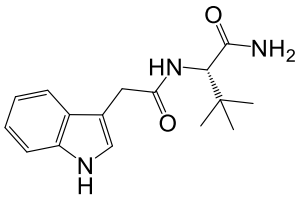
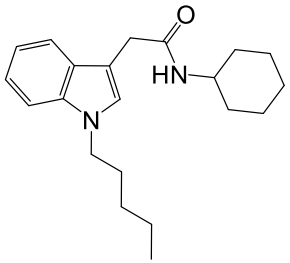
5F-Cumyl-PeGaClone		5-Fluoro analogue of Cumyl-PeGACLONE	Similar potency and efficacy to Cumyl-PeGACLONE [Janssens et al., 2020]	First identified in Germany in 2016 and reported to the EMCDDA in 2017 [EMCDDA, 2017]. Considered a significant contributor to 4 deaths in that country between 2018 and 2019 [Giorgetti et al., 2020]	Detected in 3 different drug products (herbal materials) analysed by Eurofins in September 2022.
5Cl- Cumyl-PeGaClone		5-Chloro analogue of Cumyl-PeGaClone	No information identified.	Identified in Singapore in 2018 [Hashimi et al., 2021].	No reports of detection in the UK.
Cumyl-CH-MeGaClone		Cyclohexylmethyl moiety on the indole nitrogen	Similar high potency and efficacy to Cumyl-PeGaClone and 5F-Cumyl-PeGaClone [Hashimi et al., 2021].	First identified in a police seizure of herbal material in Hungary in September 2018; subsequently also detected in several urine samples for abstinence control in Germany and within criminal or infringement procedures in Hungary. In one German lab it was detected in urine samples collected for abstinence screening between July and October 2019, while in Hungary it was identified in biological samples (urine and/or blood) from 134 cases between October 2018 and September 2019 [Haschimi et al., 2021].	No reports of detection in the UK.

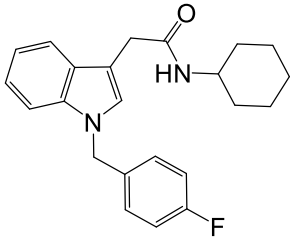
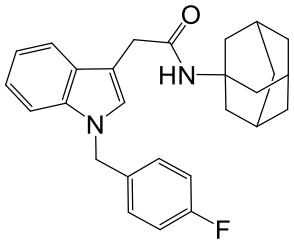
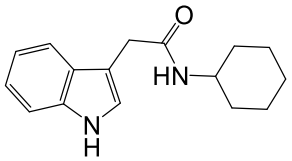
Cumyl-CB-MeGaClone		Cyclobutylmethyl on the indole nitrogen	No information identified.	notified to the EMCDDA by Hungary in June 2020 First identified in Hungary in April 2020. [EMCDDA, 2021].	No reports of detection in the UK.
Cumyl-NB-MeGaClone		Norbornyl derivative. Also referred to as Cumyl-BC-HP-MeGaClone-221	No information identified.	Formally notified to the EMCDDA on behalf of Germany in September 2020 [EMCDDA, 2021].	No reports of detection in the UK.
Materials containing a methylnorbornyl tail					
Cumyl-NBMICA		Norbornyl Tail structure	No information identified	Notified to the EMCDDA in December 2020	No reports of detection in the UK.
Cumyl-NBMINACA		Norbornyl Tail structure	No information identified	Reported to the EMCDDA by Germany in February 2021.	No reports of detection in the UK.

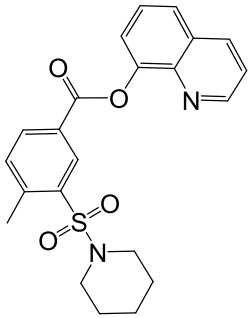
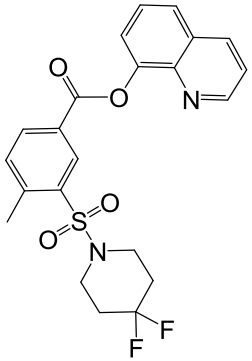
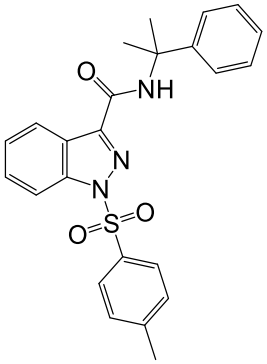
"Oxizid" compounds					
BZO-HEXOXIZID		Also referred to as MDA-19	Human CB_1 and CB_2 receptor agonist with higher binding affinity for the CB_2 receptor. Its pharmacology differs in rats where it acts as an agonist at CB_1 receptors but functions an inverse (or protean) agonist at CB_2 receptors [Diaz et al., 2008; Xu et al., 2010]. Least potent and efficacious of the "Oxizid" compounds studied [Deventer et al 2022b].	Detected in Spain in October 2016. Also reported in Singapore [UNODC 2022] and the USA [NPS Discovery 2021a] during 2021.	Detected by Eurofins Forensic services in 3 drug seizures (powders and herbal materials) between December 2021 and May 2022. Detected by LGC in blood or urine from a single case (March 2022)
BZO-POXIZID		Also referred to as 5C-MDA-19 or Pentyl-MDA-19	Full CB_1 receptor agonist and partial CB_2 receptor agonist, all with lower CB_1 potency when compared to the older compounds JWH-018 and CP55,940 [Diaz et al., 2008; More potent CB_1 agonist than BZO-HEXOXIZID [Deventer et al., 2022b].	Identified in seized materials in China, Singapore Indonesia and the USA during 2021 (Liu et al., 2022; NPS Discovery 2022; UNODC 2022]. Reported to the EMCDDA by Bulgaria in 2021.	Detected in 5 drug seizures (herbal materials) analysed by Eurofins Forensic services between February and November 2022. Identified by LGC Ltd in blood or urine from 4 clinical cases presenting between January and April 2022.

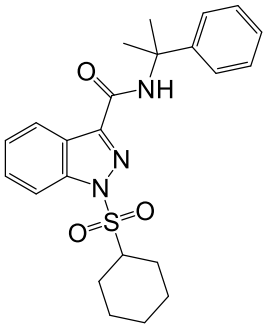
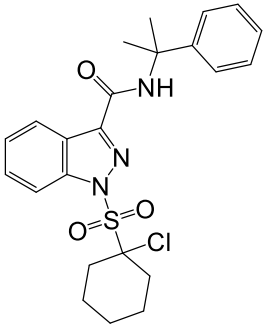
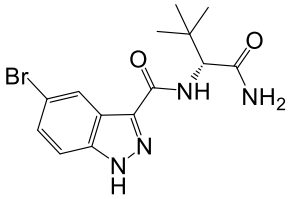
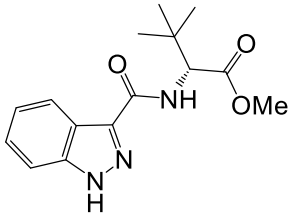
BZO-4en-POXIZID		Also referred to as 4en-pentyl MDA-19	As BZO-POXIZID, but less potent at CB1 receptors [Deventer et al 2022b].	Reported to the EMCDDA by Hungary in November 2021.	Detected in 2 drug seizures (herbal materials) analysed by Eurofins Forensic services in in November and December 2021. Identified by LGC Ltd in blood or urine from one case (March 2022). Detected in 1 drug seizure reported by the National Crime Agency and OHID during 2021. Detected in a Scottish Prison in June 2022.
BZO-5F-POXIZID		Also referred to as 5F-MDA-19 or MDA-19 5-flouropentyl analogue.	Similar CB1 receptor potency to BZO-POXIZID with higher CB2 potency [Deventer et al. 2022b].	Identified in Europe, the USA and China during 2021	Detected in 2 drug seizures from analysed by Eurofins Forensic services in February and June 2022. In both cases the drug was Impregnated onto paper. Detected in 2 drug seizures reported by the National Crime Agency and OHID during 2021.
BZO-CHMOXIZID		Also referred to as CH-MDA-19 or MDA-19 cyclohexyl-methyl derivative.	As BZO-POXIZID. Highest CB_1 and CB_2 receptor potency of the Oxizid compounds studied [Deventer et al 2022b].	Identified in Europe and Singapore in 2021	Detected in 5 drug seizures (powders, herbal materials, impregnated papers) analysed by Eurofins Forensic services between October 2021 and July 2022, as well as in 4 drug seizures reported by the National Crime Agency and OHID during 2021. Confirmed in 2 samples collected from prisons (one paper and one powder sample) and identified tentatively in a further 5 drug samples analysed by FEWS/DSTL.

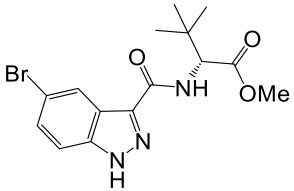
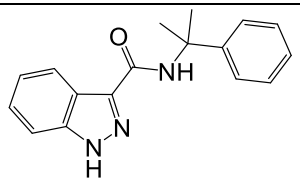
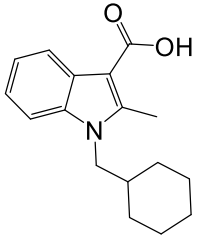
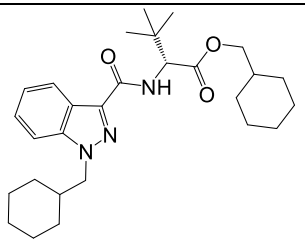
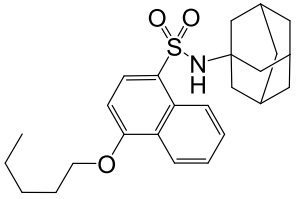
Hydroquinoline core					
ADB-FUBHQUCA			No information available	Identified in powder seized by Turkish customs in September 2021.	No reports of detections in the UK.
Thiazole-containing linkage					
PTI-3		Indole-3-thiazole SCRA	No information available	First notified to the EMCDDA from Hungary in June 2020.	No reports of detections in the UK.
Acetamide linkages					
ADB-FUBIACA		Indole-3-acetamide core-linker scaffold Also referred to as ADB-FUBIATA	Several 1- or 6-substituted derivatives have shown lower affinities for the CB_1 and CB_2 cannabinoid receptors compared with their indole-3-carboxamide analogues [Pasquini et al., 2012; Deventer et al., 2022a].	Reported for the first time in China [Liu et al., 2022; Pasin et al., 2022] Europe (Germany) and the USA [NPS Discovery 2021b] during 2021	Eurofins identified ADB-FUBIACA in 17 drug seizures between March and November 2022, including in powders and herbal materials and also impregnated onto paper. Identified in a single sample of brown powder submitted to WEDINOS in June 2022. Also tentatively identified in 2 samples analysed by FEWS.

			moderate potency and efficacy at CB1; CB2, antagonist at high concentrations		
ADB-IACA*		Acetamide-containing SCRA with no tail. Also referred to as ADB-IATA	Several 1- or 6-substituted derivatives have shown lower affinities for the CB_1 and CB_2 cannabinoid receptors compared with their indole-3-carboxamide analogues [Pasquini et al., 2012]	Detected in a Hungarian Police seizure (powder) in October 2021..	Tentatively identified in one drug seizure analysed by Eurofins in October 2022 (awaiting confirmation).
CH-PIACA		CH-PIATA	Several 1- or 6-substituted derivatives have shown lower affinities for the CB_1 and CB_2 cannabinoid receptors compared with their indole-3-carboxamide analogues [Pasquini et al., 2012; Weakly active at CB1/CB2 receptors [Deventer, unpublished].	Reported for the first time in powder seized by Spanish customs in February 2022. Powder also confiscated by The Danish Customs Agency in February 2022 [Pasin et al., 2022]. Detected by NPS Discovery in the USA in April 2022	Eurofins identified CH-PIACA in 8 drug seizures analysed since February 2022, including in powders, liquids and herbal materials and also impregnated onto paper. LGC Ltd have identified CH-PIACA in blood or urine samples from 5 clinical cases presenting between March and July 2022. The IONA study identified this SCRA in blood or urine from 3 patients presenting to an East Midlands hospital between March and June 2022. All 3 reported polydrug use, in 2 cases including smoking of ‘mamba’. Multiple other psychoactive substances were detected in each sample, including other SCRA in all 3 cases and these compounds may have contributed to the toxicity observed. Two patients had severely reduced level of

					consciousness with respiratory acidosis in one and hypothermia in the other. The third case had a slightly reduced level of consciousness associated with confusion. All 3 recovered quickly and were discharged from hospital within 20 hours.
CH-FUBIACA		CH-FUBIATA	Several 1- or 6-substituted derivatives have shown lower affinities for the CB_1 and CB_2 cannabinoid receptors compared with their indole-3-carboxamide analogues [Pasquini et al., 2012; Deventer et al., 2022a].	Detected in a Spanish customs seizure (powder) in February 2022. Also reported by NPS Discovery in June 2022. Detected in the Russian Federation in July 2022 [AIPSIN Monitoring 2022].	No reports of detections in the UK.
A-FUBIACA		Adamantyl-linked group. Also referred to as A-FUBIATA	No information available	Detected in herbal material seized by Hungarian police in January 2022.	Detected in a Police seizure from London analysed by Eurofins Forensic services in June 2022.
CH-IACA*		Indole core, cyclohexyl-linked group, acetamide linker (ACA) CH-IATA, with no tail*	No information available	Detected in powder seized by German police in March 2022.	No reports of detections in the UK.
Sulfonyl tails					

QMPSB		Arylsulfonamide -based SCRA	Potent CB_1 and CB_2 receptor agonist [Lambeng et al, 2007].	Detected in Australia between 2011 and 2012 [Blakey et al., 2016].	No reports of detections in the UK
2F-QMPSB		2-Fluoro derivative of QMPSB	No information available	First notified to the EMCDDA from Italy in January 2019.	No reports of detections in the UK
Cumyl-TsINACA		Thermal instability makes this compound less attractive for illicit use [Pulver et al 2022].	Full CB_1 receptor agonist with relatively low potency.	First identified in August 2021 in Germany from analysis of seized herbal blends.	No reports of detections in the UK

Cumyl-CHSINACA			No information available	Identified in material (paste) seized in Hungary in September 2021.	No reports of detections in the UK
CUMYL-1Cl-CHSINACA			No information available	Identified in material (paste) seized by Hungarian police in September 2021	No reports of detections in the UK
"No tail" compounds					
ADB-5Br-INACA		5-Bromo indazole carboxamide + 3,3-DiMe-butylamide	No information available	Identified in material seized in Hungary in September 2021 and in material received by NPS Discovery in the USA in November 2021 and analysed in May 2022.	Detected in a drug seizure analysed by Eurofins Forensic services in July 2022 (herbal material).
MDMB-INACA		Analogue of MDMB-4en-PINACA, but lacking the pentyl tail	No information available	Identified in powders seized by Swiss police in January 2022 and French customs in March 2022.	No reports of detections in the UK

MDMB-5Br-INACA		5-Br-indazole acetamide + 3,3-DiMe methyl butanoate	Unpublished data has suggested that curtailed Br-INACA compounds do have some cannabinoid receptor activity	Identified in plant-like material received by NPS discovery in March 2022 and analysed in May 2022 [NPS Discovery, 2022]. Also identified in New Zealand [Know Your Stuff New Zealand 2022].	Detected in 6 drug seizures (powders, herbal material) analysed by Eurofins Forensic services since April 2022.
Cumyl-INACA		Indazole carboxamide + cumyl	No information available	Identified in herbal material, seized by German Police in November 2020.	No reports of detections in the UK
Others					
M-CHMIC		Possible intermediary for the synthesis of MDMB-CHMICA	No information available	Notified to the EMCDDA by Ireland in March 2015.	No reports of detections in the UK
CHM-MDMB-CHMINACA		Cyclohexylmethyl indazole carboxamide + CHM 3,3-diMe-butanoate	No information available	Notified to the EMCDDA from Germany in April 2021.	No reports of detections in the UK
A-PONASA		Incorporates an adamantyl linked group (A), a pentoxy tail (PO), napthyl core (NA) and sulfonamide linker (SA)	No information available	Identified in pale pink powder seized by Swedish customs in December 2021 and also in white powder en route from China seized in Bulgaria in September 2021.	No reports of detections in the UK

*ADB-IACA and CH-IACA are both acetamide-containing compounds, but they also have no tail and could also be listed in the ‘no tail’ group.

Annex B: List of acronyms used in this report.

ACMD	Advisory Council on the Misuse of Drugs
DSTL	Defence Science and Technology Laboratory
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EU-MADNESS	European-wide, Monitoring, Analysis and knowledge Dissemination on Novel/Emerging psychoactive
FEWS	Forensic Early Warning System
IONA	Identification of Novel Psychoactive Substances
LGC Ltd	Laboratory of the Government Chemist Ltd
MDA	Misuse of Drugs Act 1971
MDR	Misuse of Drugs Regulations 2001
MHRA	Medicines and Healthcare products Regulatory Agency
NCA	National Crime Agency
NISRA	Northern Ireland Statistics and Research Agency
NPSAD	National Programme on Substance Abuse Deaths
NPS	New Psychoactive Substance
NRS	National Records of Scotland
OHID	Office for Health Improvement and Disparities
ONS	Office for National Statistics
PSA	Psychoactive Substances Act 2016
SCRA	Synthetic cannabinoid receptor agonists
THC	Tetrahydrocannabinol
UK	United Kingdom
UNODC	United Nations Office on Drugs and Crime
WEDINOS	Welsh Emerging Drug & Identification of Novel Substances
WHO	World Health Organization

Annex C: Proposed revised wording of the generic definition

Misuse of Drugs Act 1971 - paragraph 1(ca) of Part 2 of Schedule 2

Note: Similar changes will also be required for the Misuse of Drugs Regulations 2001 (paragraph 1 (ld) of Schedule 1) and the Misuse of Drugs (Designation) (England, Wales and Scotland) Order 2015 (paragraph 1(sa) of Schedule 1)

Changes from the November 2019 version are shown in bold and underlined.

Any compound (not being a compound for the time being specified in sub-paragraph (c) above) structurally related to 1-pentyl-3-(1-naphthoyl) indole (JWH-018), in that the four sub-structures, that is to say the indole ring, the pentyl substituent, the methanone linking group and the naphthyl ring are linked together in a similar manner, whether or not any of the sub-structures have been modified, and whether or not substituted in any of the linked sub-structures with a benzyl or phenyl group and whether or not such compound is further substituted to any extent with alkyl, ***cycloalkyl****, alkenyl, alkoxy, halide, haloalkyl or cyano substituents and, where any of the sub-structures have been modified, the modifications of the sub-structures are limited to any of the following, that is to say-*

(i) Replacement of the indole ring with indane, indene, indazole, pyrrole, pyrazole, imidazole, benzimidazole, ***9H-carbazole with the linking group attached at the 3-position****, pyrrolo[2,3-b]pyridine, pyrrolo[3,2-c]pyridine or pyrazolo[3,4-b]pyridine;*

(ii) Replacement of the pentyl substituent with ***hydrogen****, alkyl, alkenyl, benzyl, cycloalkylmethyl, cycloalkylethyl,* ***(bicyclo[2.2.1]heptan-2-yl)methyl****,* ***sulfonyl****, (N-methylpiperidin-2-yl)methyl, 2-(4-morpholinyl)-ethyl or (tetrahydropyran-4-yl)methyl;*

(iii) Replacement of the methanone linking group with an ethanone, carboxamide, carboxylate, methylene bridge, ***ethanamide*** *or methine group;*

(iv) Replacement of the 1-naphthyl ring with 2-naphthyl, phenyl, benzyl, adamantyl, cycloalkyl, cycloalkylmethyl, cycloalkylethyl, bicyclo[2.2.1]heptanyl, 1,2,3,4-tetrahydronaphthyl, quinolinyl, isoquinolinyl, 1-amino-1-oxopropan-2-yl, 1-hydroxy-1-oxopropan-2-yl, piperidinyl, morpholinyl, pyrrolidinyl, tetrahydropyranyl or piperazinyl;

Any compound structurally derived from carbolin-1-one (2,5-dihydro-1H-pyrido[4,3-b]indol-1-one) by substitution at the nitrogen atom of the indole ring by alkyl, alkenyl, benzyl, cycloalkylmethyl, (bicyclo[2.2.1]heptanyl)methyl, cycloalkylethyl, (N-methylpiperidiny-2-yl)methyl, 2-(4-morpholinyl)ethyl or (tetrahydropyran-4-yl)methyl and by substitution at the nitrogen of the pyridine ring by 1-naphthyl, 2-naphthyl, phenyl, benzyl, adamantyl, cycloalkyl, cycloalkylmethyl, bicyclo[2.2.1]heptanyl, 1,2,3,4-tetrahydronaphthyl, quinolinyl, isoquinolinyl, 1-amino-1-oxopropan-2-yl, 1-hydroxy-1-oxopropan-2-yl, piperidinyl, morpholinyl, pyrrolidinyl, tetrahydropyranyl or piperazinyl, whether or not such compound is further substituted to any extent with alkyl, cycloalkyl, alkenyl, alkoxy, halide, haloalkyl or cyano substituents;

Any compound structurally derived from N-(2-oxoindolin-3-ylidene)benzohydrazide by substitution at the indole nitrogen by alkyl, alkenyl, benzyl, cycloalkylmethyl, (bicyclo[2.2.1]heptanyl)methyl, cycloalkylethyl, (N-methylpiperidiny-2-yl)methyl, 2-(4-morpholinyl)ethyl or (tetrahydropyran-4-yl)methyl whether or not such compound is further substituted to any extent with alkyl, cycloalkyl, alkenyl, alkoxy, halide, haloalkyl or cyano substituents;

Any compound structurally derived from 3-(aminosulfonyl)benzoic acid by replacement of the benzoic acid hydrogen by 1-naphthyl, 2-naphthyl, phenyl, benzyl, adamantyl, cycloalkyl, cycloalkylmethyl, bicyclo[2.2.1]heptanyl, 1,2,3,4-tetrahydronaphthyl, quinolinyl, isoquinolinyl, 1-amino-1-oxopropan-2-yl, 1-hydroxy-1-oxopropan-2-yl, piperidinyl, morpholinyl, pyrrolidinyl, tetrahydropyranyl or piperazinyl, whether or not the aminosulfonyl nitrogen forms part of a cyclic structure, whether or not such compound is further substituted to any extent with alkyl, cycloalkyl, alkenyl, alkoxy, halide, haloalkyl or cyano substituents;

Any compound structurally derived from 3-(aminosulfonyl)benzamide by substitution at the benzamide nitrogen by 1-naphthyl, 2-naphthyl, phenyl, benzyl, adamantyl, cycloalkyl, cycloalkylmethyl, bicyclo[2.2.1]heptanyl, 1,2,3,4-tetrahydronaphthyl, quinolinyl, isoquinolinyl, 1-amino-1-oxopropan-2-yl, 1-hydroxy-1-oxopropan-2-yl, piperidinyl, morpholinyl, pyrrolidinyl, tetrahydropyranyl or piperazinyl, whether or not the aminosulfonyl nitrogen forms part of a cyclic structure, whether or not such compound is further substituted to any extent with alkyl, cycloalkyl, alkenyl, alkoxy, halide, haloalkyl or cyano substituents*;***

Annex D: ACMD membership at the time of publication

Dr Kostas Agath	Consultant psychiatrist (addictions), Change Grow Live Southwark
Professor Judith Aldridge	Professor of criminology at the University of Manchester
Professor Owen Bowden-Jones	Chair of Advisory Council on the Misuse of Drugs, Consultant psychiatrist, Central North-West London NHS Foundation Trust
Dr Anne Campbell	Lecturer in Social Work, Queens University Belfast
Dr Emily Finch	Clinical Director of the Addictions Clinical Academic Group and Consultant Psychiatrist for South London and Maudsley NHS Trust
Mr Mohammed Fessal	Chief pharmacist, Change Grow Live
Professor Sarah Galvani	Professor of social research and substance use at Manchester Metropolitan University
Mr Lawrence Gibbons	Head of Drug Threat (Intelligence Directorate, Commodities), National Crime Agency
Dr Carole Hunter	Lead Pharmacist, Alcohol and Drug Recovery Services NHS Greater Glasgow and Clyde and Doping Control Officer, UK Antidoping
Dr Hilary Hamnett	Associate Professor in forensic science, University of Lincoln
Professor Graeme Henderson	Professor of pharmacology at the University of Bristol
Professor Roger Knaggs	Associate professor in clinical pharmacy practice at the University of Nottingham

Professor Tim Millar	Professor of substance use at the University of Manchester
Mr Rob Phipps	Former head of Health Development Policy Branch, Department of Health, Social Services and Public Safety, Northern Ireland
Dr Ann Sullivan	Consultant physician in HIV and sexual health
Mr Harry Shapiro	Director – DrugWise
Dr Paul Stokes	Senior clinical lecturer in mood disorders, King's College, London
Dr Richard Stevenson	Emergency medicine consultant, Glasgow Royal Infirmary
Professor David Taylor	Professor of psychopharmacology, King's College, London
Professor Simon Thomas	Emeritus professor of clinical pharmacology and therapeutics, Newcastle University
Dr Derek Tracy	Medical director of West London NHS Trust
Dr David Wood	Consultant physician and clinical toxicologist, Guys and St Thomas' NHS Trust
Ms Rosalie Weetman	Public Health Lead (Alcohol, Drugs and Tobacco), Derbyshire County Council

Annex E: ACMD NPS Committee membership, at time of publication

Dr Kostas Agath	ACMD Member	Consultant psychiatrist (addictions), Change Grow Live, Southwark
Mr Paul Bunt	ACMD Co-opted Member	Director of Casterton Event Solutions Ltd, Former Drug Strategy Manager for Avon and Somerset Constabulary
Dr Anne Campbell	ACMD Member	Reader in substance use and mental health and co-director of the Drug and Alcohol Research Network at Queens University Belfast
Mr Peter Cain	ACMD Co-opted Member	Drugs Scientific Advisor, Eurofins Forensic Services
Dr Caroline Copeland	ACMD Co-opted Member	Lecturer in Pharmaceutical Medicine at King's College London, and the Director of the National Programme on Substance Abuse Deaths
Mr John Corkery	ACMD Co-opted Member	Senior Lecturer in Pharmacy Practice at University of Hertfordshire; mortality and epidemiological lead for EU-MADNESS project
Mr Lawrence Gibbons	ACMD Member	Head of drug threat – National Crime Agency Intelligence Directorate – Commodities
Dr Hilary Hamnett	ACMD Member	Associate Professor in Forensic Science, University of Lincoln
Professor Graeme Henderson	ACMD Member	Professor of Pharmacology at the University of Bristol

Professor Stephen Husbands	ACMD Co-opted Member	Professor of Medicinal Chemistry, University of Bath
Professor Roger Knaggs	ACMD Member	Associate Professor in clinical pharmacy practice at the University of Nottingham
Professor Fiona Measham	ACMD Co-opted Member	Professor and chair in criminology, University of Liverpool; co-founder and co-director, the Loop
Mr Harry Shapiro	ACMD Member	Director – DrugWise
Dr Richard Stevenson	ACMD Member	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Ann Sullivan	ACMD Member	Consultant physician in HIV and sexual health
Professor Simon Thomas	ACMD Member	NPS Committee Chair, Emeritus Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Mr Ric Treble	ACMD Co-opted Member	Retired Laboratory of the Government Chemist (LGC) expert
Dr Derek Tracy	ACMD Member	Medical director of West London NHS Trust
Dr Mike White	ACMD Co-opted Member	Former Forensic Intelligence Adviser
Dr David Wood	ACMD Member	Consultant physician and clinical toxicologist at Guy's and St Thomas' and reader in clinical toxicology at King's College London

Annex F: Quality of evidence

Range of evidence

Evidence gathered was considered in line the ACMD's standard operating procedure for quality of evidence [ACMD, 2020b].

To evidence the identification and prevalence in the UK of the new SCRA considered in this report, the ACMD's NPS Committee wrote to stakeholders requesting available data on the substances listed in Annex A. Responses were received from the following (which include submissions of 'no data held' and anecdotal evidence:

External agencies:

- EU-MADNESS project
- NCA
- NPSAD
- TICTAC Communications Ltd
- Eurofins forensics
- LGC Assure
- WEDINOS
- IONA study

Government departments:

- Office for Health Improvement and Disparities
- Border Force Intelligence Analysis (Home Office)
- FEWS (Defence Science and Technology Laboratory)
- MHRA

This report also draws on evidence from peer-reviewed literature (UK and international publications) and government reports. The ACMD also considered international approaches when drafting its recommendations.

Quality of evidence (design, limitations, bias)

For the SCRA referred to in this report, evidence of their availability and harm has been sought, allowing the ACMD to make an informed recommendation on their classification and schedule.

Many agencies and departments returned 'no data held' for most of the compounds considered in this report. It is important to note that owing to the 'novelty' of all of these substances, forensic testing is limited and inconsistent across the UK and as a result, information being fed into reporting agencies that were approached will not be representative. This is supported by anecdotal reports. As reports have identified the majority of these substances elsewhere in Europe, there is potential availability of these substances in the UK.

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